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Original Communications

ON THE DEVELOPMENT OF THE EARLY HUMAN OVUM, WITH SPECIAL REFERENCE TO THE TROPHOBLAST OF THE PREVILLOUS STAGE: A DESCRIPTION OF 7 NORMAL AND 5 PATHOLOGIC HUMAN OVA*

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THE purpose of this paper is to describe the early morphologic development of the normal human trophoblast and to compare it with corresponding phases in the development of abnormal ova. The observations recorded encompass a period beginning shortly after implantation of the blastocyte, on about the seventh day, and extending to about the fourteenth day when chorionic villi appear; this time interval coincides with the twenty-first to the twenty-eighth day of the normal menstrual cycle; that is, the week preceding the first missed period of the pregnancy. In addition, one villous embryo of 16.5† days is included for the sake of completeness.

*Read at a meeting of the Chicago Gynecological Society, Chicago, Ill., December 18, 1942.

This study has been aided by grants from the Carnegie Corporation of New York, the William F. Milton Fund of Harvard University, and the Committee for Research in Problems of Sex, National Research Council.

†The ages of the ova are recorded as mean values on the basis of coital dates in the particular case and/or comparative embryologic development in the macaque; for example, the figure 16.5 indicates that this ovum is judged to be between 16 and 17 days old.

In studying the early development of the human ovum, one is confronted by the complicating fact that, whereas many problems in embryology can be approached or even solved through comparative investigation of lower forms, the problem of early human placentation must be studied directly with human material. This is due to the scarcity of comparative material among subhuman forms, for in but one other primate family besides man, that of the anthropoid apes, has been discovered the so-called *interstitial* type of implantation[1] in which the blastocyst becomes completely embedded within the compact tissue of the endometrium. The only anthropoid specimen described in the literature which is comparable to the material considered in the present paper is the 10.5-day old chimpanzee ovum, "Yerkes A," reported by Elder, Hartman and Heuser.[2] Obviously, since in their study but one stage was described, information as to this type of implantation has been up to now incomplete. Indeed, the sole detailed description of placentation in any primate is the classic one of Wislocki and Streeter[3] on the monkey (*Macaca mulatta*). However, implantation in the macaque differs from that of man and the higher apes, since it is of the *superficial* type; i.e., the blastocyst embeds on the endometrium and thereby remains in the cavity of the uterus during gestation.

For practical purposes, the situation in the human being is not actually diverse from that in the macaque, for although the human blastocyst, as has been mentioned above, buries itself in the endometrium and hence thereafter no longer theoretically occupies the uterine cavity, it does in reality effect the anatomic obliteration of the lumen after about the third month.

Material and Methods

The material used in this study consists of 12 fertilized ova (7 normal and 5 abnormal) discovered in surgically removed uteri at the Free Hospital for Women during the past five years. The clinical group from which these specimens were obtained has been discussed previously,[4] as have also various other clinical, pathologic, and embryologic aspects pertaining to the material.[4-8]

Procedure.—The uterus is opened laterally under saline or Locke's solution and the uterine cavity is closely inspected with a four-power binocular dissecting microscope in an effort to recover a free blastocyst.* The endometrium is then carefully examined under fluid prior to fixation by means of the low-power binocular dissecting microscope. If an implanted ovum is not found, Bouin's fixative is gently pipetted over the endometrial surface while the specimen is still immersed in salt solution, and the endometrium is re-examined with low-power binocular vision.

It is significant that the youngest specimen thus far observed, the 7.5-day ovum, was discovered only after this complete technique had

*The fluid is pipetted off and examined under the microscope. Also, in the event that the ovum may not yet have entered the uterus, the Fallopian tube corresponding to the ovary containing the most recent corpus luteum is routinely flushed, and the collected fluid is carefully examined in every case.

been employed. The other specimens were found prior to fixation, either with the naked eye immediately upon opening the uterus, or by low-power binocular inspection. Fixation greatly helps to accentuate contours and irregularities of the endometrium and thus serves to reveal the implanted ovum even though the vascular response which would have facilitated detection is not yet discernible by low-power examination of the fresh specimen.

Following fixation for 36 hours in Bouin's fluid, the endo- and myometrium surrounding the ovum may be blocked out into a cube, approximately 15 mm. in all diameters. Some uteri, however, are frontally sectioned after 6 hours so that a slab of endomyometrium, 10 to 15 mm. thick, is removed. This favors fixation of the specimen from below, as well as from above. The ovum, situated near or on the surface, becomes fixed almost immediately, but the deeper parts of the endometrium require longer treatment.

At this point, Doctor Chester H. Heuser, of the Department of Embryology of the Carnegie Institution of Washington, takes charge of the material and faultlessly sections the embryo and the adjacent implantation site serially at 6μ, using the double embedding method of celloidin followed by paraffin. This technique has been described more fully elsewhere.[6]

Each serial section is then photographed by Mr. O. O. Heard on 35 mm. film and enlarged on bromide paper to a diameter necessary for reconstructions. The illustrations for this paper have been kindly prepared by Mr. Chester Reather.

We are greatly indebted to these workers for cooperating in this study, and to Doctors George L. Streeter and George W. Corner for their kind help in interpreting these specimens.

I. Normal Ova

Table I summarizes the menstrual, coital, and associated pertinent data relating to the 7 normal conceptuses (5 previllous and 2 villous) to be described in the order of age as follows:

A. Previllous Stages

1. *The 7.5-Day Specimen (Mu-8020)**

Low-Power Examination Prior to Section.—This ovum was discovered by use of the four-power dissecting binocular microscope after partial fixation of the endometrial surface. When its location had been established in this way, it was barely visible to the naked eye, measuring 0.46 by 0.42 mm. After complete fixation, it appeared as a slightly raised, oval area (Fig. 1*A*) the long diameter of which lay in the vertical axis of the uterus. Within the center of the slightly elevated region was a round opaque zone, the embryonic mass, 0.07 mm. in diameter. When viewed with extremely oblique light, the embryo appeared to be covered by a thin membrane, the abembryonic wall of the ovum. At the periphery, this membrane merged with a thickened opaque rim (Figs. 1*B* and 1*C*), the result of trophoblastic development of the ovum where it came in contact with the endometrium.

*These specimens are designated by letters and numbers, the latter referring to the accession number of the specimen in the Carnegie Embryological Collection.

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TABLE I. NORMAL OVA

CASE CARN. NO.* AGE GRAVIDA PARA	MEAN ESTIMATED AGE OF OVUM (DAYS)	DAY OF CYCLE ON WHICH OPERATION TOOK PLACE	ENDOMETRIAL DATING	DAY OF PROBABLE FERTILE COITUS	RANGE OF DAYS ON WHICH CTA. BEGAN	GROSS FINDINGS		
						SIZE AND APPEARANCE OF UTERUS	ENDOMETRIUM	LOCATION OF IMPLANTATION SITE AND OF OVARY CONTAINING ACTIVE CORPUS LUTEUM (C. L.)‡
A: *Previllous*								
Mu-8020 38 yr. x ix	7.5	24	22	16	28, 32(2^w)† 31 (1^m)	1½ x enlarged; marked retroflexion	Pale; edematous; 3 to 5 mm. thick; congested and hemorrhagic areas, probably traumatic in origin, at fundus	3 mm. from fundus, 7 mm. from left C. L. Right
Wi-8004 29 yr. vi vi	9.5	25	26	15	34 (1^w) 34 (1^m)	Slightly enlarged; moderately firm; cervix lacerated, everted and eroded; myometrium 20 mm. thick (av.)	Numerous recent petechial hemorrhages scattered over both surfaces of endometrium	At right cornu 3 mm. from fundus, 10 mm. from right uterine border C. L. Right
Si-7699 35 yr. iv iii	11.5	25	25	12	26 to 29 (6^w)	Cervix moderately eroded; myometrium 18 to 22 mm. thick	Pale lavendar, except for congested area around ovum; 3 to 4 mm. thick	In midline, 6 mm. from top of uterine cavity C. L. Left

Re-7950 32 yr. iv iv	12.0	26	23	13	27 to 33 (7^{w}) 27 to 35 (6^{m})	1½ x enlarged; cervix showed moderate circumoral erosion; myometrium 16 to 22 mm. thick	Edematous, pale, lavender-gray; 5 mm. thick (av.)	11 mm. from fundus, 10 mm. from left C. L. Right
Al-7700 34 yr. ix viii	12.5	29	26	15	33 to 36 (4^{m}) LMP^{w}	Markedly lacerated and eroded cervix, with irregularity at the junction of the portio and endocervix; myometrium contained many thickened and tortuous vessels	Pale; slightly convoluted	8 mm. from left, 21 mm. from fundus C. L. Right
B: *Villous*								
Ru-7801 33 yr. ix vii	13.5	28	26	--§	24 to 28 (4^{w}) 24 to 28 (8^{m})	Slightly enlarged; myometrium normal except for thickened, tortous vessels on cut surface	Lavender to bluish-gray; surface somewhat irregular; 5 to 6 mm. thick	20 mm. from fundus, 10 mm. from right C. L. Right
Bu-7802 37 yr. ix ix	16.5	33	28	16	26, 33 37, 42¶ (4 ? ^{w} or ^{m}) LMP^{w}	1½ x enlarged	1 cm. area of erosion on anterior portion of endocervix	10 mm. from left, 16 mm. from fundus C. L. Right

*The accession numbers of the Carnegie Institution of Washington are used to designate these specimens.

†Parentheses enclose number of cycles studied; ^{w} indicates menstrual dates were from a written record; ^{m} indicates menstrual dates were from memory.

‡All normal ova were found on the posterior wall of the uterus.

§There were no accurately recorded coital dates in this case.

¶The long cycles occurred following birth of baby (7 months preceding operation).

The latter, in general, had a "chicken-skin" appearance, due to the prominent gland mouths interspersed along the flattened, stretched-out epithelial surface. This picture was in marked contrast to that of older endometria (associated with ova seen in Figs. 2*A* to 7*A*) which tend to assume a progressively developing so-called "pig-skin" appearance, the appellation given to full-blown decidua.

Sectioned Specimen.—The ovum at this stage consists of a superficially but well-attached flattened blastocyst the trophoblast of which has proliferated only at the embryonic pole where the ovum is in contact with the endometrium. It should be noted here, as will be borne out in all specimens described subsequently, that trophoblast develops only where it has adequate contact with maternal tissue. The endometrial epithelium is absent (probably digested) at the implantation site. Damage to the immediately adjacent epithelium is evidenced by the clear, hydropically degenerated nuclei at the junction of the ovum and the surface epithelium. (The surface epithelium is not completely regenerated until about the nineteenth or twentieth day of ovular development, or until approximately a week after the first missed period.)

There is a slight vascular response to the presence of the recently implanted ovum. The endometrium, as noted in Table I, is in the twenty-second day of its cyclic development (Fig. 1*B*).

(a) *Trophoblast.*—The trophoblast appears as a thick, saucer-shaped mass composed of two main types of cells, the *syncytiotrophoblasts* and the *cytotrophoblasts;* there are also transitions between these two varieties (Fig. 1*C*). The abembryonic pole of the ovum still consists of the thin, flattened, mesothelium-like cells which characterize the wall of the primate blastocyst prior to implantation.[9] This type of cell metamorphoses rather abruptly into the large polyhedral form seen at the margin of the trophoblastic disc. In the monkey blastocyst, this initial metamorphosis, just after implantation, results in a syncytium, but from the human material available, the nature of these first changes in man is not entirely clear. Apparently, however, the process is quite similar in the human being, because many of the least differentiated cells at the junction of the blastocyst wall have indistinct boundaries and resemble a syncytium, although others possess definite membranes.

i. *Syncytiotrophoblast.*—The syncytiotrophoblast, comprising the bulk of the trophoblastic disc, is peripherally situated and is composed of cells of widely variegated appearance. The earliest form is apparently the single, massive, deeply staining cell with an extremely large and hyperchromatic nucleus. A pair of such cells is seen at the extreme right in Fig. 1*C*. Various transitions are found between this type of

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Fig. 1.—The 7.5-day ovum, Mu-8020. *A.* A gross view of the specimen and surrounding endometrium, photographed under fluid. The mouths of the endometrial glands are evident as tiny dark spots, each of which is surrounded by a concentric circle. The superficially implanted ovum appears in the center of the picture as a light opaque ring containing the embryonic mass. The dark ring around the embryo represents the chorionic cavity, while the opaque outer ring represents the double layer of trophoblast at the periphery of the ovum, due to collapse of the blastocyst (See Fig. 1*C*). ×35.

B. A general medium-power view of the recently implanted ovum and associated endometrium. The latter is in the twenty-second day of its cycle (morphologically) and shows active secretion of glands and marked physiologic edema of its stroma. ×100.

C. A detailed view of the mid-cross section of the ovum and underlying endometrium. The ovum is well attached by its trophoblast at the embryonic pole, although it is so shallowly implanted at this stage that almost half the ovum is exposed and therefore still shows the characteristics of the blastocyst wall at the abembryonic pole. The primitive character of the trophoblast is evident; the large, dark multinucleated masses represent primitive syncytiotrophoblast, whereas the relatively small, light discrete cells represent the primitive cytotrophoblast. The embryo is the globular mass in the center of the flattened, chorionic cavity and shows the primitive entoderm above and the primitive ectoderm below. The primordium of the amniotic cavity is the tiny cleft between the primitive ectoderm and the trophoblast. ×300.

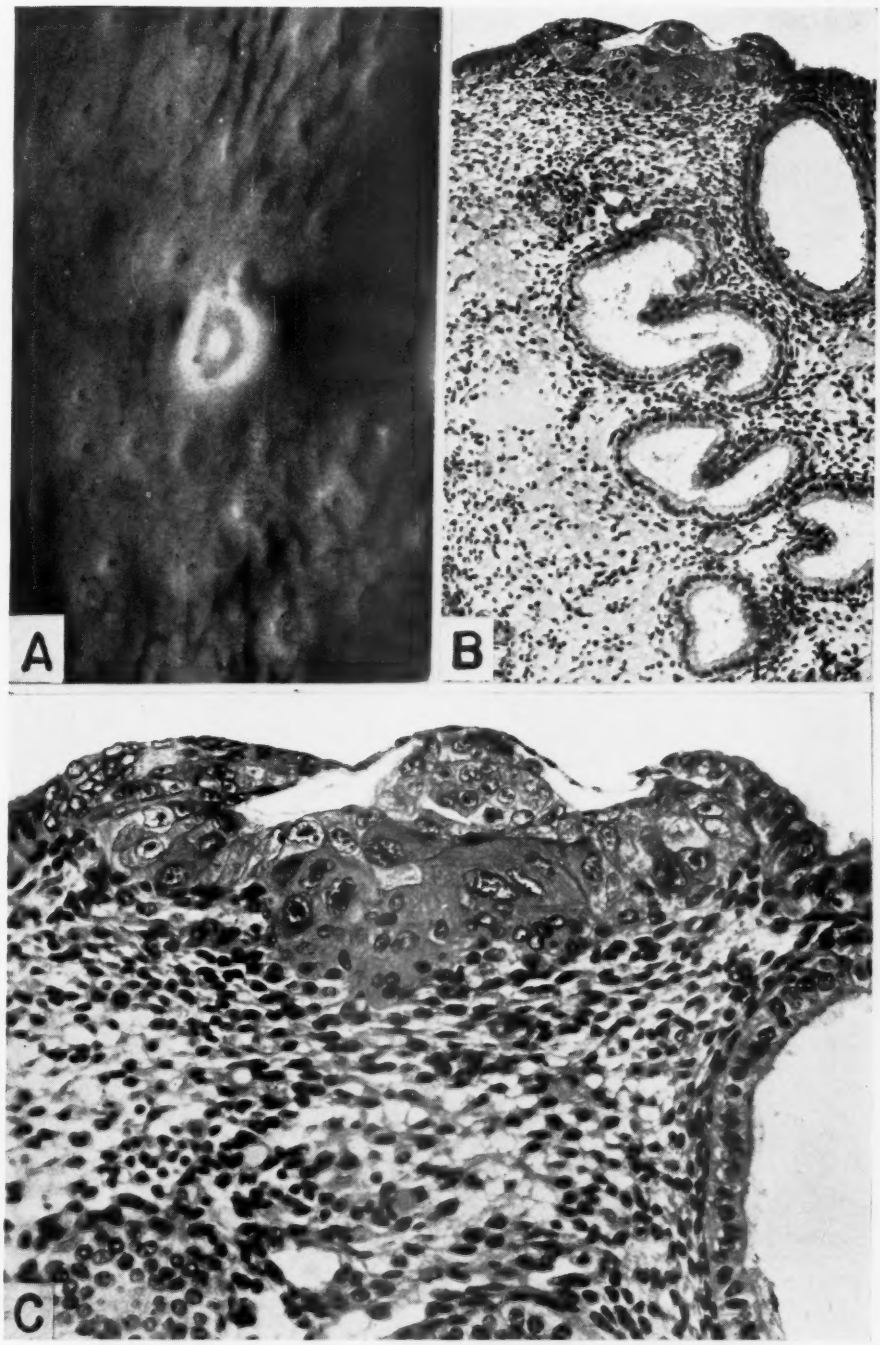

Fig. 1.—For legend see opposite page.

cell and the enormous, dark syncytium containing numerous pleomorphic nuclei lying just beneath the embryonic mass (Fig. 1*C*). The large hyperchromatic nuclei are the progenitors, whereas the smaller, more mature, nuclei are descendants, apparently derived by amitotic division, since no mitoses are evident anywhere in the syncytiotrophoblast.

The syncytiotrophoblast presents a very uneven surface to the adjacent endometrial stroma. The latter is being invaded by irregular trophoblastic pseudopodia which are in the process of surrounding and digesting small masses of the stroma—presumably to nourish the growing ovum. Two such localized areas of endometrium are seen in Fig. 1*C*.

ii. *Cytotrophoblast.*—The cytotrophoblast, on the other hand, is much less prominent and consists of large, irregular, pale staining, polyhedral cells lying nearest the chorionic cavity (the cavity of the ovum). Their cell boundaries are distinct in contrast to those of the mature syncytiotrophoblast, although the initial stage in the formation of the latter is a single, large, dark cell. Whether the syncytiotrophoblastic cell is a modified cytotrophoblastic cell or whether both types develop independently when trophoblast first forms after implantation, remains to be determined by further investigation.

(b) *Embryo.*—As seen in Fig. 1*C*, the embryo proper consists of a flattened globular mass composed of two types of cells: (i) the small dark ones of the superficially situated primitive entoderm; and (ii) the larger, pale, polyhedral cells of the ectoderm. Within the latter germ layer, is a cleft-like amniotic cavity the maximum diameter of which is 24μ.

Age of Ovum and Time of Nidation.—Since the single and therefore unquestionably fertile coitus in this case took place 7.5 days prior to laparotomy, the conceptus cannot be older than this time interval, although it may be younger.* The latter, however, is not likely in view of its developmental age. Since the trophoblastic growth may have been going on for possibly as long as 48 hours, embedment may be tentatively estimated to have occurred in a 5.5-day old embryo, or on the sixth day of development. The endometrium at the time of implantation would then have been in the twentieth day of its cyclic development. On the basis of comparative studies, we had not been led to expect that nidation could take place so early, for, in the monkey, Streeter and his co-workers[9] had reported its occurrence on the eighth or ninth day of ovular development.

*This is in the event that at the time of coitus ovulation had not yet taken place, and that therefore fertilization was delayed pending the release of the egg.

Fig. 2.—The 9.5-day ovum, Wi-8004. *A.* A gross surface view of the implantation site photographed under fluid. The ovum is now fairly well implanted; the dark, irregularly oval area in the center represents the exposed portion of the ovum, whereas the opaque peripheral ring represents the portion of the ovum covered by endometrial epithelium. Elsewhere the latter is becoming wrinkled with resulting obliteration of gland mouths. ×22.

B. A medium-power view of the now fairly well-implanted ovum and underlying endometrium. The latter, in the twenty-sixth day of its cycle, shows moderate predecidual change of its stroma and a "saw-toothed" contour of its secretory glands. ×100.

C. A detailed view of a mid-cross section of the ovum and its immediately surrounding endometrium (same section as Fig. 2*B*). Some epithelial repair of the implantation site has occurred, although a portion of the ovum is still exposed. The prominent feature of the trophoblast, at this stage, is the presence of many anastomosing lacunae within the syncytiotrophoblast. The latter is surrounding and eroding maternal sinusoids which will supply blood to the trophoblastic lacunae. The embryo, still a bilaminar germ disc, shows a moderately well-developed amniotic cavity (below) which is being enclosed by amniogenic cells being derived from, and still attached to, the adjacent trophoblast. ×200.

2. *The 9.5-Day Specimen (Wi-8004)*

Low-Power Examination Prior to Section.—Upon inspecting the uterine lining, a tiny, raised, red spot, 0.28 mm. in diameter, was discovered, situated as noted in Table I. Around two-thirds of this central point there appeared a zone of brilliant red hemorrhage and/or congestion, the total diameter of the area measuring 0.85 mm.

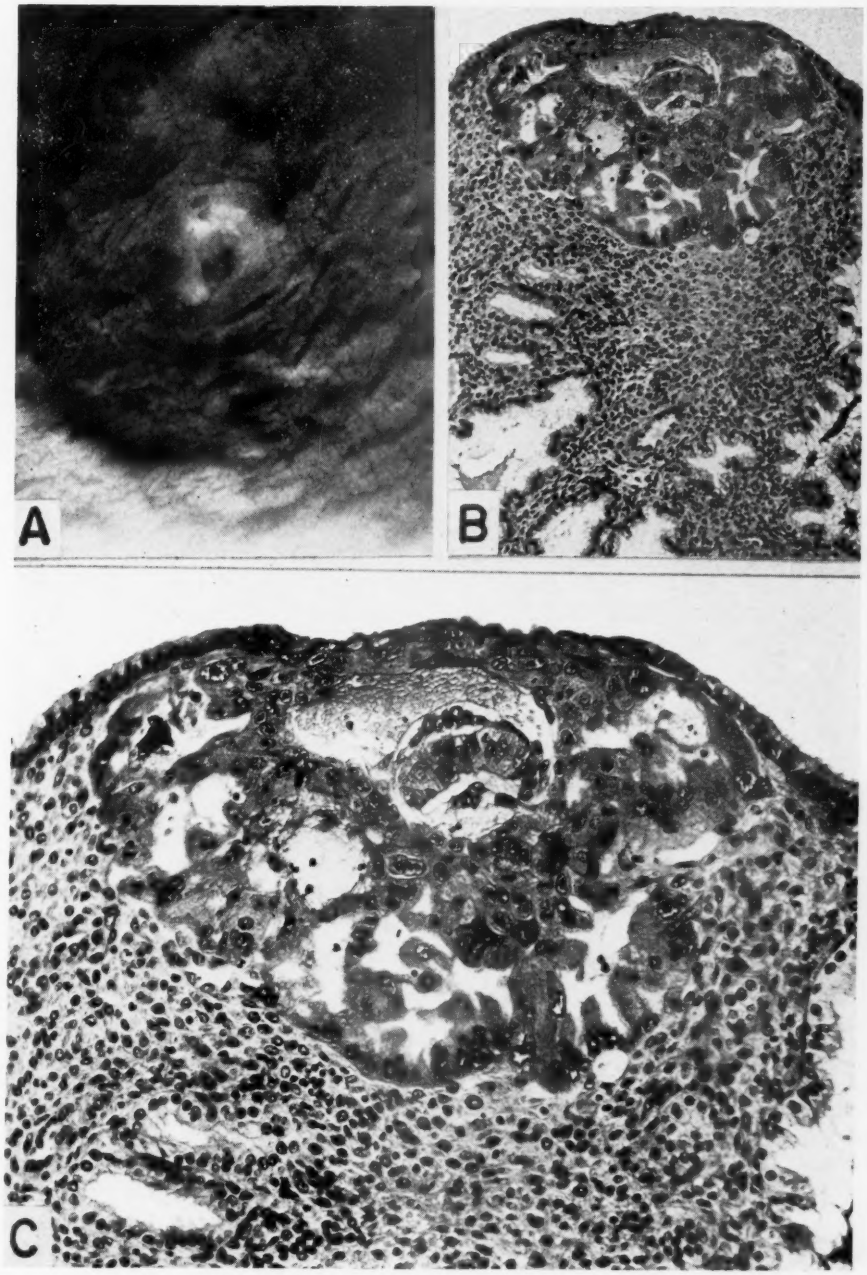

Fig. 2.—For legend see opposite page.

After complete fixation, the implantation site (Fig. 2*A*) showed an oval, raised area, 1.0 by 0.69 mm. in diameter, the long axis of which was parallel to that of the interstitial portion of the right tube. This elevation rose 0.26 mm. above the surrounding endometrium; at its apex an oval defect in the endometrium, 0.36 by 0.21 mm. in diameter, exposed the ovum immediately underlying the surface. The elevation, therefore represented the partially implanted conceptus over which the endometrial epithelium had begun to regenerate.

The surrounding endometrium was much more mature than that associated with the 7.5-day ovum previously described. The surface was markedly wrinkled and the mouths of the glands were represented by small, irregular slits.

Sectioned Specimen.—The embryo at this stage is approximately two-thirds implanted, the defect in the endometrium being partially epithelialized. There are no recognizable elements of the original blastocyst remaining, as was the case in the 7.5-day conceptus; i.e., the thin abembryonic wall.

The endometrium is typical of the twenty-sixth day of cyclic development (Fig. 2*B*), except that the degree of secretory activity is greater than is encountered in the corresponding stage of the nonpregnant menstrual cycle. This finding agrees with Sturgis'[10] observations of hypersecretory activity in early pregnant endometria. In response to the presence of the ovum, vascular sinusoids are developing from branches of spiral arterioles. The predecidual, or early decidual reaction is only slightly more marked immediately around the ovum than elsewhere (Fig. 2*B*).

(a) *Trophoblast.*—While the entire wall of the ovum shows some degree of trophoblastic development, this is naturally more prominent at the embryonic than at the abembryonic pole (Fig. 2*C*).

i. *Syncytiotrophoblast.*—The most conspicuous feature of the trophoblast is the presence of numerous syncytiotrophoblastic lacunae which receive the maternal blood and constitute the future intervillous space of the placenta. Most of these lacunae are intercommunicating, while a few small ones are still isolated. Several of them already contain maternal blood conveyed to the ovum by the developing endometrial sinusoids. In one instance, a lacuna is seen to have ruptured into the chorionic cavity, allowing the escape of maternal blood therein. This feature, while pathologic, is probably not significant. It accounts for the tiny red spot observed in the fresh specimen. Likewise, the area of hemorrhage partially surrounding the central red point was due to the presence of maternal blood in the trophoblastic lacunae. Later on, during the eleventh and twelfth days of development, most of the lacunae become filled with blood which appears as a brilliant hair-line circle around the periphery of the ovum, especially when the latter is superficially implanted.

ii. *Cytotrophoblast.*—The cytotrophoblast is relatively insignificant at this stage and consists of the irregular layer of cells immediately about the chorionic cavity. These are in the process of forming a few primitive mesoblasts, the forerunners of the placental connective tissue elements, vascular as well as supportive. This stage in both the human being and the monkey has been described in some detail by one of the authors (A. T. H.)[11] in 1935.

(b) *Embryo.*—The embryo, or germ disc, while still of bilaminar form with its ventrally situated plate of primitive entoderm and its

dorsally located ectoderm, does show some advance over the younger stage. The amniotic cavity is more pronounced and appears as a space dorsal to the embryo proper.* The amnion, as in the 11.5- and 12.5-day specimens, is arising in situ from the adjacent cytotrophoblast.

Age of Ovum.—On the basis of the degree of development, the probable fertile mating took place 9.5 days prior to operation. Correlation of other subsequent coital dates with the degree of development shows that the conceptus cannot be older than 9.5 days, but it may be slightly younger, if the ovum were not available for immediate fertilization after insemination.

3. *The 11.5-Day Specimen (Si-7699)*

This ovum, as well as the 12.5-day stage (Al-7700) has already been described in detail by the authors,[6] but they are included in this report in order to present in full the various phases of previllous ovular development illustrated by the material available in our study as a whole.

Low-Power Examination Prior to Section.—The ovum appeared as an oval, translucent spot, 0.84 by 0.91 mm. in diameter, with its long axis parallel to that of the uterus (Fig. 3*A*).

The endometrium overlying the ovum rose 0.14 mm. above the general endometrial surface and showed an irregular, cross-like defect from which exuded a tiny, clear mass of coagulum (Fig. 3*B*). Surrounding the ovum was an irregular, hemorrhagic and/or congested area of endometrium measuring 6.0 by 2.0 mm., a mirror image of which appeared on the anterior wall opposite the implantation site. This was probably due to some local action of the trophoblast on the endometrium. Following fixation, these features, with the exception of the hemorrhage about the ovum, were all accentuated. The endometrium showed stellate crevices representing gland openings with the intervening surface epithelium beginning to wrinkle. The wrinkling is apparently related to the degree of predecidual reaction beneath the surface.

Sectioned Specimen.—The ovum is almost entirely buried beneath the endometrium, epithelial regeneration over it having nearly been completed.

The endometrium at the implantation site is 4.25 to 5.0 mm. thick, and, except for the presence of moderate persistent edema, is typical of the twenty-fifth day of the cycle. The spiral arterioles are very prominent, especially near the ovum (Fig. 3*C*); this is due partly to their dilatation and partly to the surrounding predecidua. There is slight predecidual reaction beneath the epithelium and about the conceptus. The latter has elicited a moderate vascular reaction which on reconstruction, takes the form of an anastomosing network of sinusoids derived from the surrounding arteriovenous capillary system. The circulation at this stage is essentially a one-way phenomenon; that is, terminal capillary twigs from the anastomosing branches drain into the lacunar network, but there is as yet neither arterial nor venous connection with the lacunae of the trophoblast.

(a) *Trophoblast.*—

i. *Syncytiotrophoblast.*—The greater portion of the trophoblastic wall is now composed of a thick peripheral shell of syncytiotrophoblast containing numerous blood-filled lacunae, most of which anastomose

*The ova are all purposely arranged upside down in the illustrations so that the endometrium is oriented in the usual fashion.

with one another. The few lacunae which have not, as yet, become incorporated into this system are those associated with trophoblast in the process of actively eroding contiguous maternal vessels. When the blood from such a vessel flows into a lacuna, the latter acts as a tiny check lock to prevent it from immediately entering the lacunar system, which it does eventually when the lacuna coalesces with its fellows. This would appear to be a safer mechanism than erosion of blood vessels with resultant direct flow of blood into the lacunar system.

ii. *Cytotrophoblast.*—The cytotrophoblast is beginning to be more prominent at this stage and appears as an inner lining of the shell of the ovum. Irregular thickenings of proliferating cytotrophoblast, the first primordia of chorionic villi, are commencing to push peripherally through the outlying syncytiotrophoblast.

(b) *Exocoelom of the Embryo and the Chorionic Cavity.*—The cavity within the ovum has now resumed the essentially spherical shape comparable to the segmentation cavity of the blastocyst prior to implantation. This cavity is called the *exocoelom* of the embryo, whereas the larger space outside, within which lies the embryo, is the *chorionic* cavity.

Lining the exocoelom of the embryo and attached to the entoderm of the germ disc, is a mesothelium-like membrane, first described by Heuser.[12] Beneath this membrane, the significance of which is not as yet understood, are numerous primitive mesoblastic cells, containing a few angioblasts, which represent the forerunners of the connective tissue elements of the placenta.

(c) *Embryo.*—The embryo proper still consists of a bilaminar germ disc, a fairly well-formed amniotic cavity, and an amnion that is still attached to the adjacent trophoblast from which it is arising.

Age of Embryo.—While fertile coitus most likely took place on the twelfth day of the cycle, 12.5 days prior to operation, the probable fertilization or developmental age is approximately 11 days, an estimate more in harmony with the embryologic development of the specimen, as well as with the probable time of ovulation in this particular patient.

4. *The 12.0-Day Specimen (Re-7950)*

Low-Power Examination Prior to Section.—The implantation site appeared in the form of a tiny red circle, 0.78 mm. in diameter, within which was a slightly bulging, transparent gray vesicle 0.43 mm. in diameter. The hemorrhagic ring represented the blood within the trophoblastic lacunae, and the vesicle represented the chorionic cavity.

Fixation revealed a shallow 0.23-mm. ulceration in the endometrial epithelium overlying the implanted ovum (Fig. 4*A*). The latter barely elevated the endometrium in this region. After the specimen had been

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Fig. 3.—The 11.5-day ovum, Si-7699. *A*, A portion of the posterior uterine wall, natural size, to show the implantation site with its surrounding zone of congestion and hemorrhage.

B. A high-power view of the endometrial surface of the implantation site. Note the opaque elevation made by the underlying ovum and the coagulum escaping from the defect in the epithelium. This triangular break in the surface is being repaired by maternal epithelium (See Fig. 3*C*). ×22.

C. A medium-power view of a section through the center of the embryo. The ovum is now well implanted and the epithelial defect nearly repaired (it is completely so in this section). The shell of the ovum is composed of an outer, lacunae-riddled syncytiotrophoblast and an inner cytotrophoblast that is proliferating to form the primordia of chorionic villi. The embryo, still a bilaminar germ disc, deviates to the right of the implantation axis. The amniotic cavity, the space below the germ disc, is more advanced than in the 9.5-day specimen. The exocoelomic membrane, attached to the edge of the germ disc, is formed from the primitive connective tissue (mesoblast) lining the chorionic cavity of the ovum. ×100.

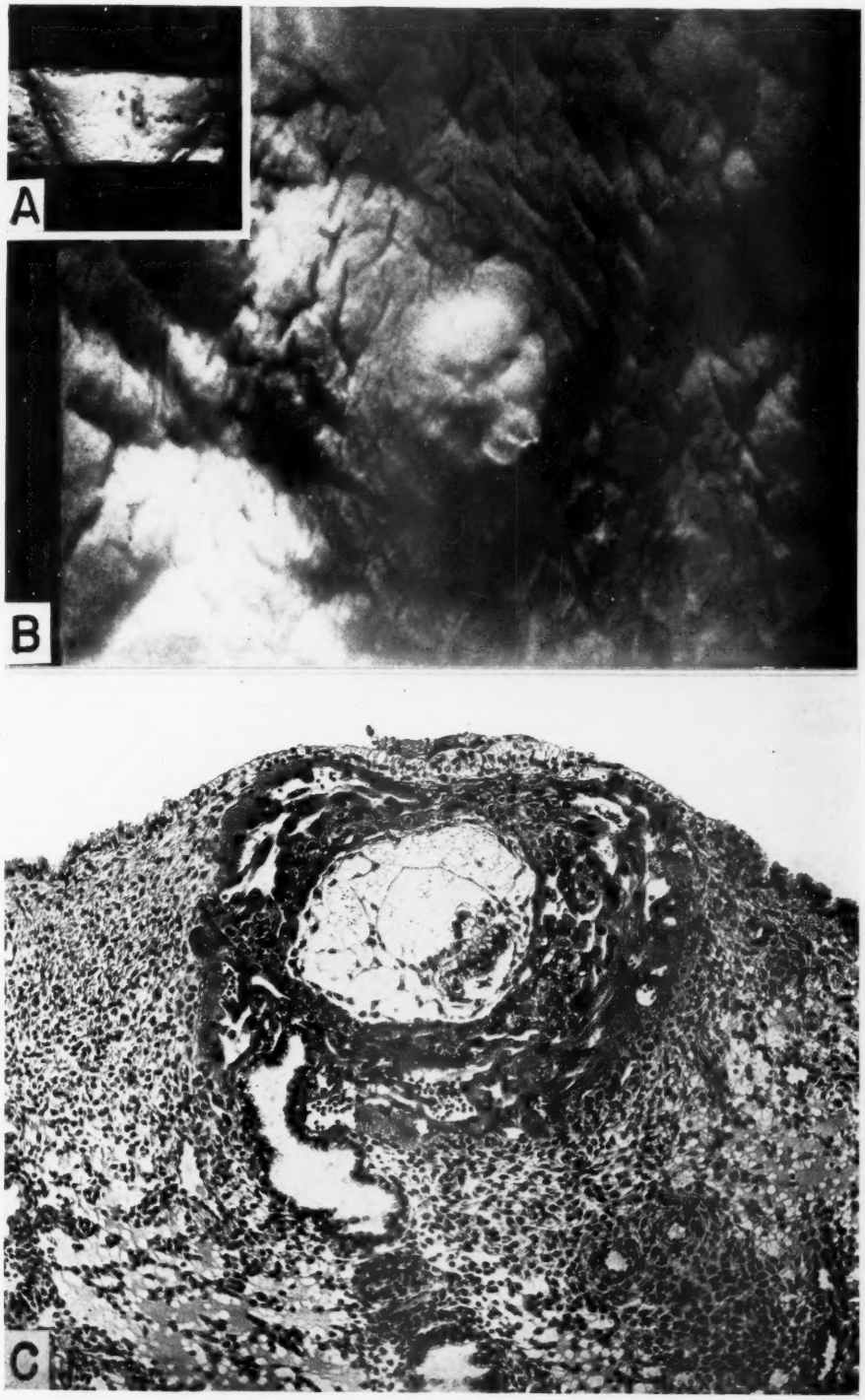


Fig. 3.—For legend see opposite page.

embedded in celloidin and cleared in cedar oil, the implanted ovum was distinctly visible, as shown in Fig. 4*B*. The vacuolated areas in the thick, peripheral shell represented the trophoblastic lacunae which were filled with maternal blood and which had been visible in the fresh specimen. The large, central cavity—the chorionic cavity of the ovum—had been observed before fixation as a gray, translucent vesicle.

The endometrium elsewhere showed evidence of edema with prominent gland mouths and a slightly bulging epithelial surface between the latter. The edema suggested a comparatively young secretory endometrium, in spite of the relative developmental maturity of the ovum.

Sectioned Specimen.—While the ovum is fairly well embedded, the epithelial regeneration of the superficial defect is comparatively scant. This specimen is a little larger and slightly more developed than the preceding one. Aside from the increase in size, the trophoblast is somewhat more mature—the lacunae are larger, more numerous and contain slightly more blood. The few primordia of the chorionic villi are also a bit more advanced in their development. The exocoelom is more mature, but the embryo itself, while in general similar to the previous specimen, is a little less differentiated, judging from the somewhat disorderly arrangement of its ectodermal cells. The germ disc, slightly asymmetric in form, is thicker at one edge than at the opposite one; the significance of this difference is not understood at the present time.

The endometrium, which is in the twenty-third day of its cyclic development, shows no predecidual reaction, in spite of the probable presence of the ovum for approximately 4 to 5 days. The conceptus has, however, elicited a moderate vascular response around itself. The glands are actively secreting, although this feature is poorly illustrated in the particular region photographed because of the edema and the relative scarcity of glands.

Age of Embryo.—The probable fertile coitus took place on the thirteenth day of the cycle, 12.5 days prior to operation. There were several subsequent coital dates within the estimated ovulation time, but had conception resulted from any of these, the ovum would have been younger than its obvious developmental age which is intermediate between the 11.5- and 12.5-day specimens; this conceptus has accordingly been dated as 12 days old.

5. *The 12.5-Day Specimen (Al-7700)*

Low-Power Examination Prior to Section.—The ovum appeared as a tiny translucent vesicle, slightly less than 1 mm. in diameter, in the midst of a hemorrhagic and/or congested area 7.0 by 10.0 mm., situated as recorded in Table I. At the periphery of the tiny vesicle was a brilliant, 0.9 mm. hair-line red circle representing the maternal blood within the trophoblastic lacunae.

Fig. 4.—The 12.0-day ovum, Re-7950. *A.* A surface view of the implantation site (photographed under fluid). The ovum is situated beneath the oval ulcer, just above the wedge-shaped area of endometrium. ×22.

B. A comparable view of the implantation site after the specimen had been cleared. The ovum is clearly seen in the center of the photograph as a white, ring-like object. The central portion represents the chorionic cavity, while the peripheral portion is the trophoblastic shell containing lacunae. ×22.

C. A mid-cross section of the ovum and surrounding endometrium. The former is in essentially the same stage of development as the ova Si-7699 (Fig. 3*C*) and Al-7700 (Fig. 5*B*). The endometrium, however, is much younger; i.e., 23 days, instead of 25 and 26 days, respectively. The ovum, therefore, either implanted at a younger stage of its development or on endometrium that was less mature than those of the above-mentioned specimens. ×100.

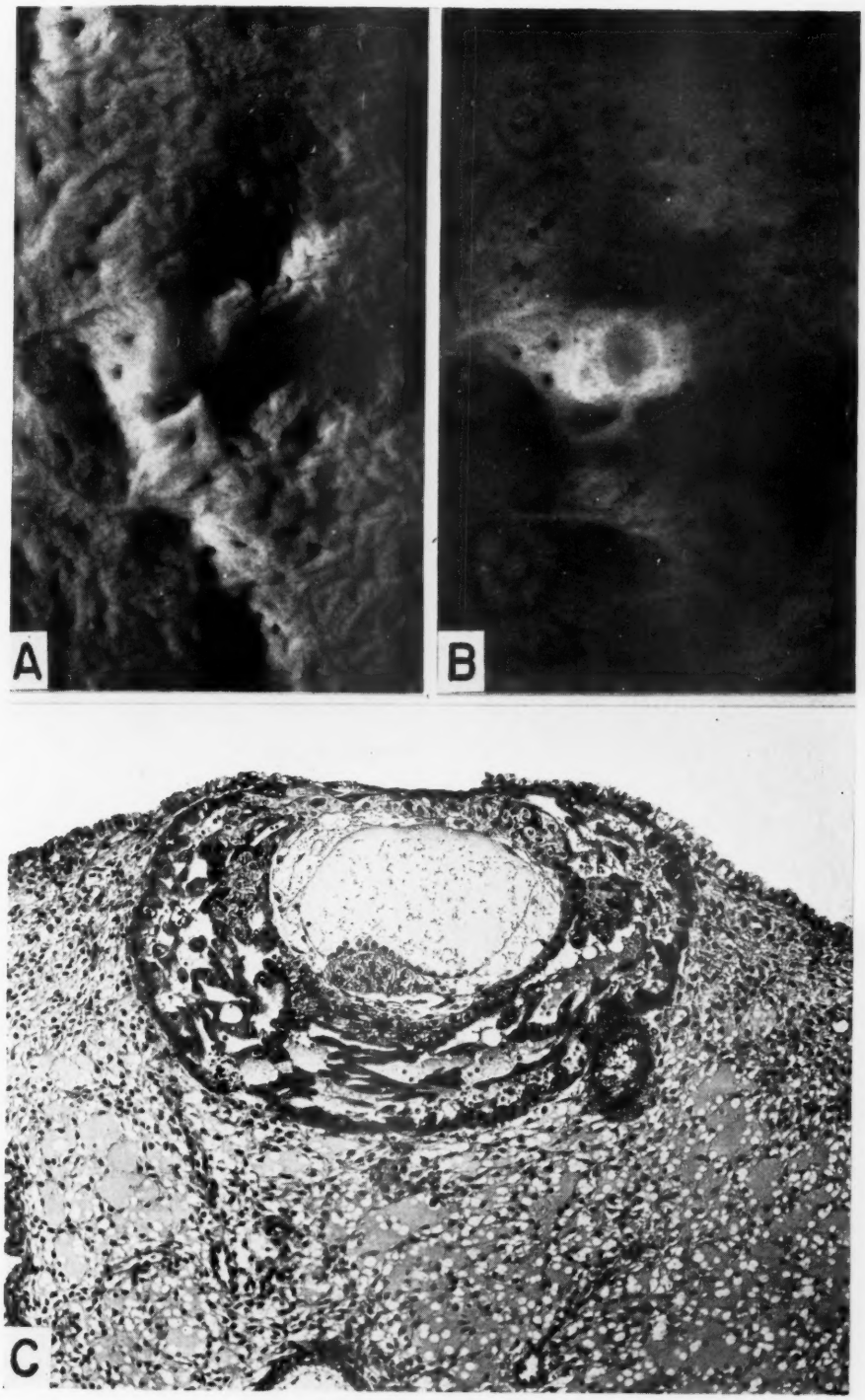


Fig. 4.—For legend see opposite page.

After fixation, the vesicle (Fig. 5*A*) measured 1.26 mm. in diameter and was raised 0.1 mm. above the surrounding endometrium. The latter showed fine wrinkling of its epithelial surface between the stellate crevices of the gland mouths.

Sectioned Specimen.—The ovum (Fig. 5*B*) is slightly more advanced in its development than the 12.0-day stage, although the embryo proper is not significantly different. The egg is less deeply implanted and hence not as completely covered by regenerating maternal epithelium. Indeed, some of the overlying tissue is necrotic, probably as a result of interference with its blood supply by the ovum underneath.

(a) *Trophoblast.*—Correlated with a more superficial implantation is a relatively poorly developed abembryonic trophoblast.

i. *Syncytiotrophoblast.*—Elsewhere the trophoblast shows large, well-filled lacunae within the peripheral syncytiotrophoblast.

ii. *Cytotrophoblast.*—The cytotrophoblast now assumes a more active role. Prominent primordia of chorionic villi, arising from the inner cytotrophoblastic shell, are growing superficially through the surrounding syncytiotrophoblast to lay the foundation for the primitive villous stage.

The endometrium, which is characteristic of the twenty-sixth day of development, shows edema, as well as a moderate predecidual and secretory reaction. Near the conceptus, the sinusoids of the endometrium are prominent and slightly congested. Hemorrhage has occurred in the endometrial stroma from nearby sinusoids, many of which have definite defects in their endothelial lining. A fairly early decidual reaction is present in the stroma about the ovum and shows mild leucocytic infiltration.

Age of Embryo.—The single and therefore undoubtedly fertile coitus took place on the fifteenth day of the cycle, 13.5 days prior to operation. Therefore the conceptus cannot be older than 13.5 days. On the basis of its morphologic development, its age has been estimated as approximately 12 to 13 days.

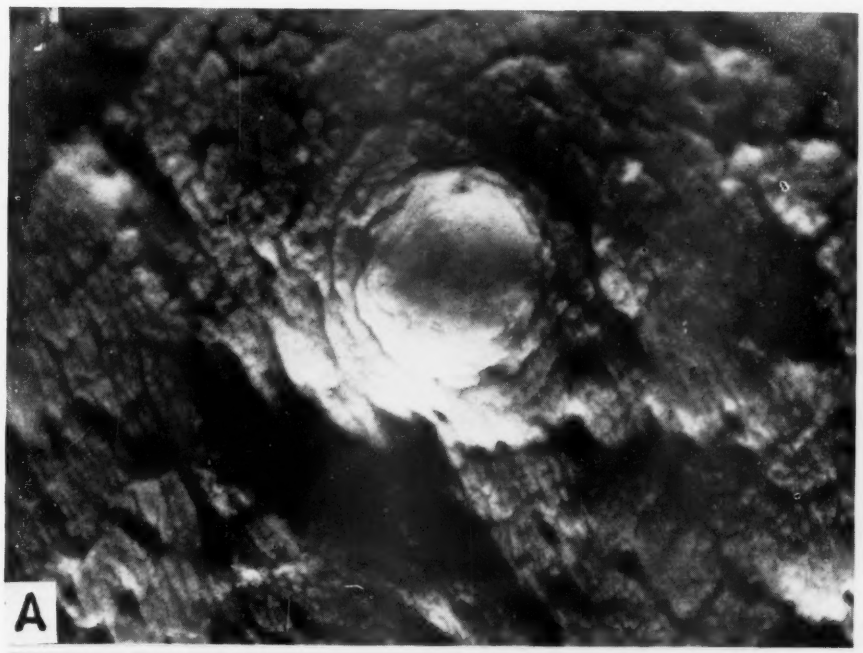
B. Villous Ova*

Two examples of the primitive villous stage (Ru-7801 and Bu-7802) will be briefly described in order to trace the development of the villous ova up to a more familiar phase of chorionic development. Also these specimens will serve for comparison with one of the pathologic ova (Br-7800) which failed to develop chorionic villi because of some defect in the trophoblast.

*These two ova are being described in detail by Doctor C. H. Heuser, of the Carnegie Institution of Washington, Department of Embryology, for publication in the near future.

Fig. 5.—The 12.5-day ovum, Al-7700. *A.* A surface view (under fluid) of the implantation site. This specimen is relatively shallowly implanted, as compared to the three previous ones (Figs. 2-4), and hence the ovum creates a more prominent elevation of the endometrium. Some of this prominence is, however, due to increasing maturity of the ovum, as also seen, for example, in the 13.5-day specimen (Fig. 6). ×22.

B. A mid-cross section of the ovum and surrounding endometrium. This specimen differs from the two preceding ones (Figs. 3 and 4) in that the primordia of the chorionic villi are more fully developed. Such primordia are best seen at "4" and "8 o'clock" as proliferations of the cytotrophoblast. An increased amount of maternal blood is present in the trophoblastic lacunae (the future intervillous space). The early decidual reaction about the ovum is slightly more advanced than in the 11.5-day specimen (Fig. 3*C*). ×100.



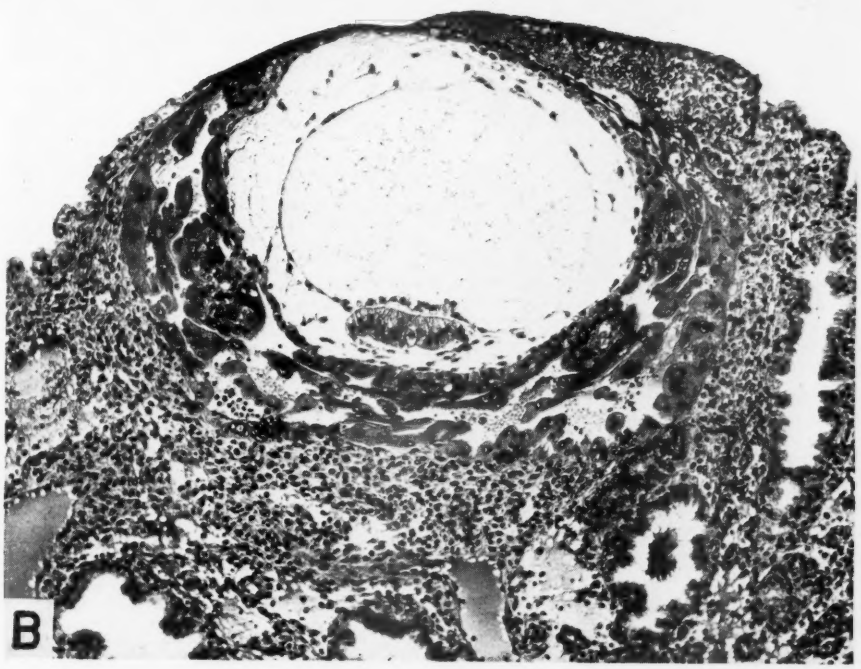


Fig. 5.—For legend see opposite page.

1. *The 13.5-Day Specimen (Ru-7801)*

Low-Power Examination Prior to Fixation.—In the fresh specimen, the implantation site appeared as a somewhat conical elevation 3.6 by 3.06 mm., surmounted by a hemorrhagic roughened area, 1.8 by 2.16 mm., from which issued a bright hemorrhagic tab measuring 2.0 by 3.0 mm.

There was no hemorrhage or congestion in the surrounding endometrium, as had been the case in both the 11.5- and the 12.5-day specimens.

After fixation (Fig. 6*A*), these various features were accentuated, except for color changes. The roughened, hemorrhagic area could now be seen to be due to a cap-like formation of fibrin and old blood clot, the so-called "Schlusscoagulum" of Peters.

The epithelial surface of the endometrium disappeared under the overhanging edge of this cap, much as the skin disappears under the edge of a moderately old scab. The surrounding endometrium showed a coarsely but irregularly convoluted surface with numerous fine wrinkles and fairly prominent stellate gland openings. The gross picture of the endometrium was suggestive of early or developing decidua.

Sectioned Specimen.—

(a) *Development of Chorionic Membrane.*—The most prominent feature in this ovum (Fig. 6*B*) is the formation of simple unbranched chorionic villi from the irregular framework of cytotrophoblast which is clothed by the syncytiotrophoblast lining the intervillous space. Active growth of the cytotrophoblast toward the periphery of the ovum is apparently displacing the remnants of syncytiotrophoblast. The latter are beginning to appear in the surrounding decidua as placental site giant cells. This portion of the implantation site has been investigated in both man and the macaque by Ramsey.[13]

There is now a distinct chorionic membrane composed of the outer syncytium and the inner Langhans' epithelial layer. The latter is adjacent to the prominent mesoblastic layer lining the chorionic cavity. In situ angio- and mesogenesis are still active in the mesenchymal tips of growing villi and, to a lesser extent, on the inner surface of the chorionic membrane.

The endometrium of the implantation site shows marked vascular response to the presence of the conceptus (Fig. 6*B*) in the form of large, thin-walled sinusoids containing relatively little blood. Hemorrhage has occurred into a dilated gland beneath the ovum, due to erosion of the epithelium by the trophoblast, followed by reflux bleeding from the intervillous space. There is marked, early decidual response about the ovum. Associated with this altered stroma, are infiltrating, placental site giant cells derived from the cast-off, early, peripheral syncytiotrophoblast. The surface epithelium is attempting to close in

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Fig. 6.—The 13.5-day ovum, Ru-7801. *A*. The surface view (under fluid) of the implantation site. The endometrium is now beginning to assume the "pigskin" appearance of decidua. The completely implanted ovum is covered by an operculum, or "Schlusscoagulum," from which fresh maternal blood is escaping. The latter is seen as the irregular tab to the right of the elevation made by the ovum. ×8.

B. A mid-cross section, low-power, of the ovum and surrounding endometrium. The chorionic villi have formed, and are either simple in type or show early branching. A considerable amount of maternal blood is within the intervillous space, having gained access therein from vessels not appearing in this photograph, as well as from the large, dilated sinusoid seen at the left. The blood beneath the ovum is within a gland, due to communication of the latter with the intervillous space. The decidua around the ovum contains many placental site giant cells, derived from the "desquamated" cells of the primitive syncytiotrophoblast. The embryo, deviating to the right of the implantation axis, now has a well-developed amnion (to the right) and yolk sac (to the left). The operculum is shown above the ovum. ×35.

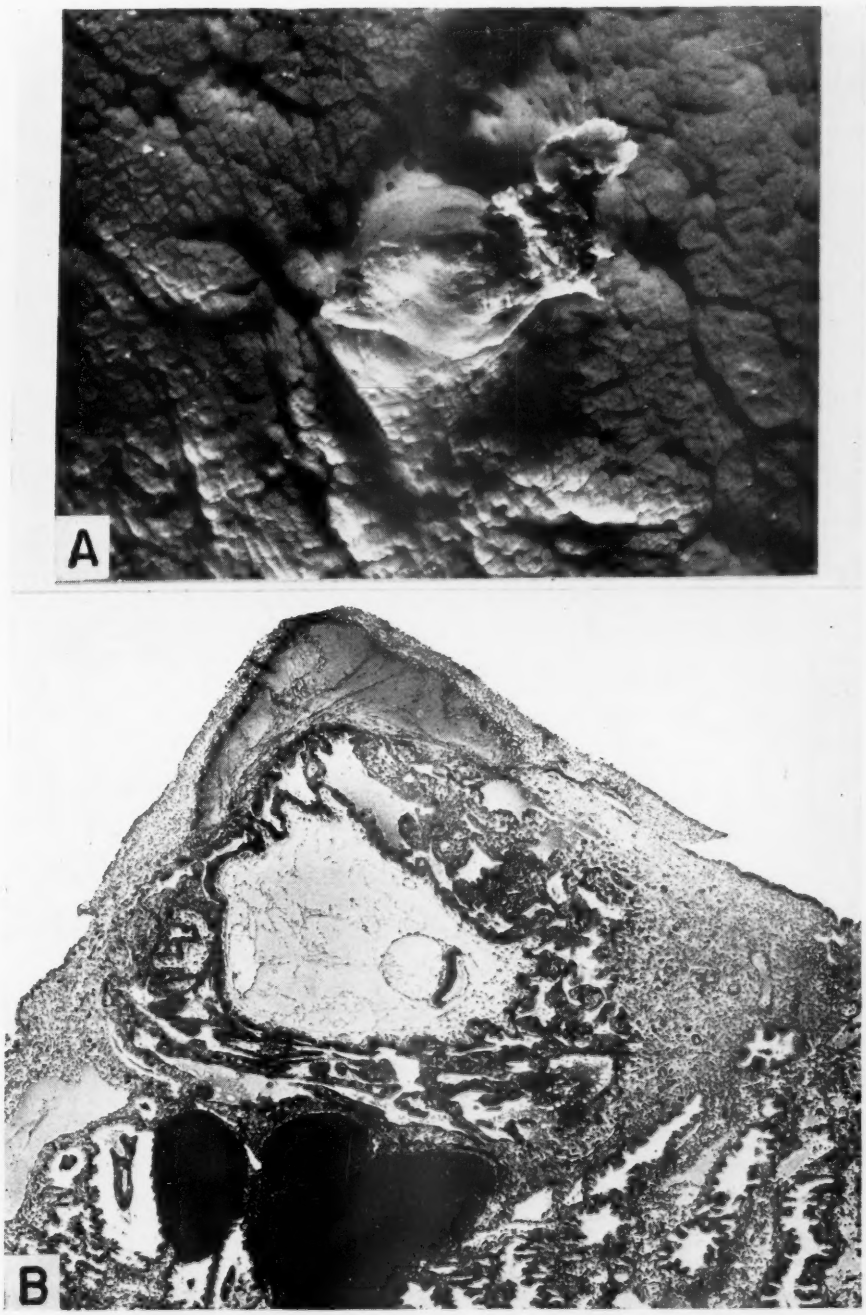

Fig. 6.—For legend see opposite page.

the defect created by the implanting ovum, but much of the embryonic pole of the latter is devoid of any covering except the "Schlusscoagulum." Beneath this is a relatively large blood space, the intervillous space, the maternal blood from which has seeped out through and under the "Schlusscoagulum" to cause the hemorrhage seen in the fresh specimen. Elsewhere, the endometrium is actively secretory, vascular, and in the stage of early but definite decidual formation about the spiral arterioles and beneath the surface epithelium.

(b) *Embryo.*—The embryo has now assumed its more familiar form and possesses a typical yolk sac and amniotic cavity. The epithelial portion, or embryonic shield, however, still consists only of a dorsal ectoderm and a ventral yolk sac entoderm.

The amnion, in places, is double-layered, as is the yolk sac, but no hematopoiesis is present in the wall of the latter. The exocoelomic membrane (Heuser's) has disintegrated, leaving several vesicular fragments within the chorionic cavity. It is thought by some (Heuser[14]) that this membrane is the primitive precursor of the yolk sac and that the latter is in some way, as yet not fully understood, derived from it. Others, including the authors, believe it to be merely the lining of the chorionic cavity, or, conversely, the boundary of the exocoelom, derived from the primitive mesoblastic cells lining the chorionic cavity.

Age of Ovum.—There were no accurately recorded coital data, but, on the basis of its morphology, this specimen, which is similar in its general development to the famous Peters' ovum, was estimated to be between 13 and 14 days of age.

2. *The 16.5-Day Specimen (Bu-7802)*

Low-Power Examination Prior to Section.—In the fresh, the ovum was seen as a slightly oval, raised, plateau-like area, measuring 5.0 by 6.0 mm. The elevated portion was slightly translucent and presented a finely mottled, hemorrhagic and/or congested appearance. Surrounding the raised area, was a collar of bright red surface hemorrhage varying from 0.7 to 2.0 mm. in width (Fig. 7*A*).

Following fixation, the "Schlusscoagulum," or closing cap, could be readily distinguished and measured 3.96 by 5.4 mm. The edges were curled up and the epithelium of the adjacent endometrium disappeared beneath the scab-like structure. The recent hemorrhage arose from beneath the edge of the latter.

The endometrium showed a moderately coarse irregularity of its surface which in general was markedly wrinkled. Gland openings were not as prominent as in previous specimens.

Sectioned Specimen.—

(a) *Chorion.*—The ovum now possesses early branching chorionic villi attached to a well-defined and moderately mature chorionic membrane (Fig. 7*B*). Discontinuous vascular primordia are present in the

Fig. 7.—The 16.5-day ovum, Bu-7802. *A*. The surface view (under fluid) of the implantation site showing the operculum, recent hemorrhage, and the early decidual reaction of the endometrium. ×6.

B. A mid-cross section of the ovum and its surrounding endometrium. This specimen differs from the preceding one (Fig. 6) in that the chorionic villi are more complex and the maternal vascular response more pronounced. Note the large, vascular sinusoid in the lower left-hand corner of the photograph. It is striking that there is comparatively little blood in the intervillous space in comparison to the size of the sinusoidal system that will ultimately supply the ovum with blood. The embryo has now lost its bilaminar character and shows what appears to be primitive streak formation with early mesoderm formation. The yolk sac is more advanced and possesses a double wall. Between the amnion and the chorion is a mass of mesenchyma—a potential amniotic duct. ×30.

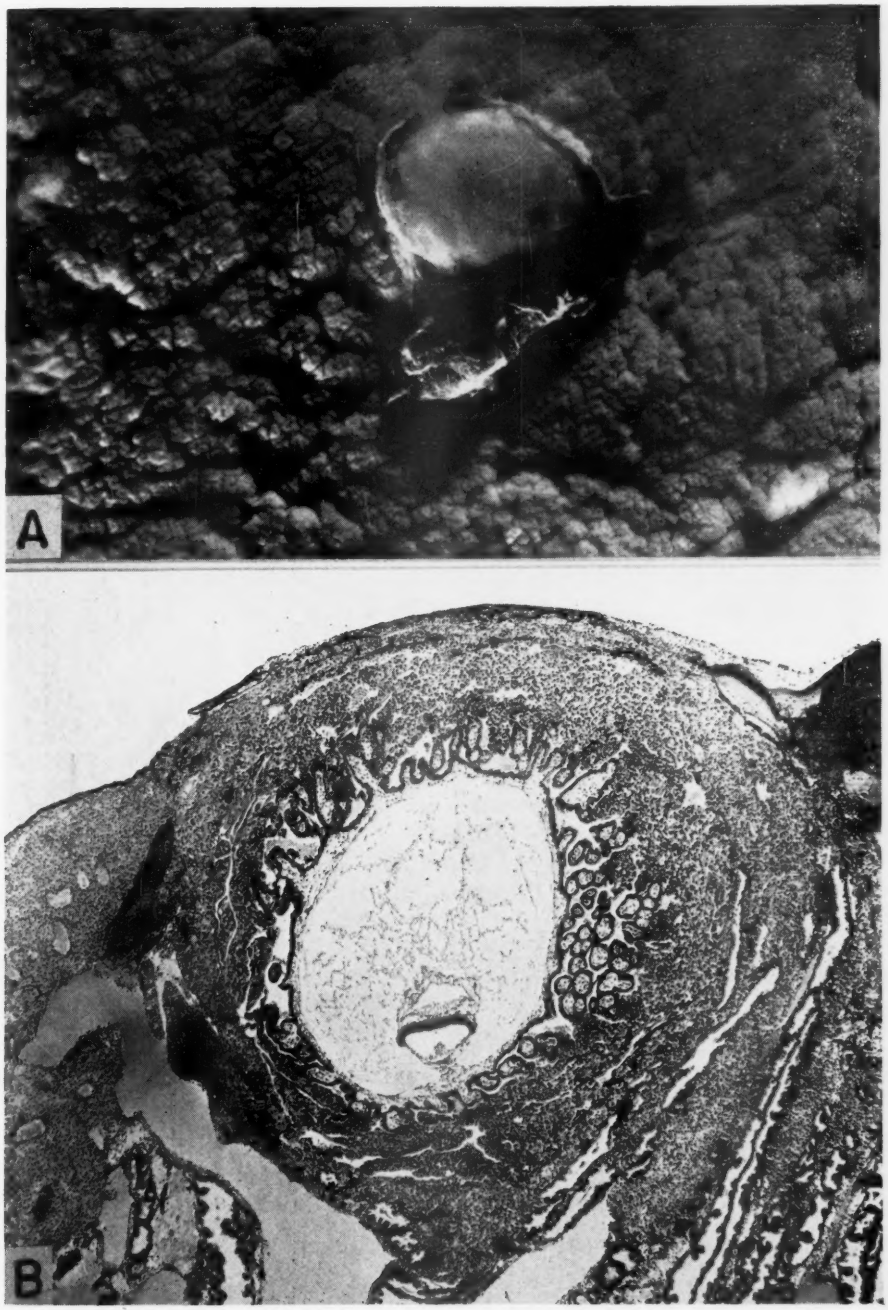

Fig. 7.—For legend see opposite page.

TABLE II. ABNORMAL OVA

CASE CARN. NO. AGE GRAVIDA PARA	MEAN ESTIMATED AGE OF OVUM (DAYS)	DAY OF CYCLE ON WHICH OPERATION TOOK PLACE	ENDOMETRIAL DATING	DAY OF PROBABLE FERTILE COITUS	RANGE OF DAYS ON WHICH CTA. BEGAN	GROSS FINDINGS		
						SIZE AND APPEARANCE OF UTERUS	ENDOMETRIUM	LOCATION OF IMPLANTATION SITE AND OF OVARY CONTAINING ACTIVE CORPUS LUTEUM (C. L.)†
Be-7771 35 yr. iv iv	--*	32	27	--*	30 to 32 (3^w)	Laceration, eversion and erosion of cervix	Polypoid; congested; 5 mm. thick (av.)	2.5 cm. from fundus and at the extreme right margin of the uterine cavity C. L. Left
Tr-7700 28 yr. vi vi	11.5	31	25	18	31, 33 (2^w) 31, 37, 41 (^{m})	1½ x enlarged; cervix lacerated, everted and eroded, with moderate irregularity of the junction between portio and endocervix	Thick (6 mm.); pale, edematous; lavender-gray; moderate numbers of irregular, stellate depressions 1 to 2 mm. in depth and 1 to 3 mm. in diam. which resembled scars	Near right cornu, 10 mm. from fundus and 7 mm. from lateral boundary C. L. Right
Er-7850 33 yr. xv xi	11.5	31	25	18	32, 34 (^{m})	Not remarkable	4 to 6 mm. thick; lavender-pale gray	13 mm. from fundus, 11 mm. from right C. L. Left
Sm-8000 29 yr. v iv	11.5	28	25	16	32, 32 (2^w)	Normal	Pale yellow; 5 mm. thick; areas of hemorrhage suggesting impending cta.	15 mm. from fundus, 5 mm. from left C. L. Left
Br-7800 35 yr. iv iv	13.5	32	26	--‡	25 to 31 (3^w)	1½ x enlarged; cervix lacerated	5 to 6 mm. thick; gray; undulating; many coarse, irregular crevices and fissures between undulations	15 mm. from fundus, 8 mm. from right border of uterine cavity C. L. Right

*Because of the extreme abnormality of this ovum and the large number of coital dates recorded, there is no way of accurately estimating the day of probable fertile coitus or the age of the egg which may be anywhere between 11.5 and 17.5 days.

†All abnormal ova were found on the anterior wall of the uterus.

‡Owing to the large number of coital dates, as well as the abnormal condition of this specimen, the day of probable fertile coitus cannot be estimated.

mesoblastic connective tissue of the chorion and its villi. The cytotrophoblast at the tips of the villi shows more progress in its peripheral growth toward the goal of ultimately forming a new shell of trophoblast to replace the early peripheral shell of syncytiotrophoblast. It would appear that the cytotrophoblast through this phase of villous formation follows the syncytiotrophoblastic framework which was formed earlier by the vacuolization of the solid syncytiotrophoblast.

Microscopically, the endometrium about the ovum, as elsewhere, shows an increasing vascularity and decidual reaction, as compared to the preceding specimen.

(b) *Embryo.*—The embryo shows some progress over the previous stage; the primitive streak is present and true mesoderm is forming. There are suggestions of vessels in the wall of the rapidly maturing yolk sac. The amnion is attached to the chorionic membrane by what appears to be an amniotic duct primordium.

Age of Ovum.—The degree of development of this conceptus is compatible with the assigned age of 16.5 days which would place conception on the third coital date recorded within the estimated ovulation time. Since, however, intercourse also took place 2 days before and 2 days after this date, the exact fertilization age cannot be established.

II. Abnormal Ova

Having outlined briefly the main features typical of the 7 early normal ova, we will go on now to consider the principal characteristics of the 5 pathologic ova recovered in the course of our investigation. No attempt will be made to assign definite developmental ages to these specimens, for, since in every case, one or more of their component structures is pathologic or even absent, it is difficult to estimate accurately their absolute or even their relative ages. However, the specimens will be described in the order of their apparent developmental ages, on the basis of clinical as well as available embryologic data. Other pertinent information relating to these specimens is summarized in Table II.

1. *A Previllous Ovum With Defective Trophoblast and Absent Embryo (Be-7771)*

Low-Power Examination Prior to Section.—Before fixation, the implantation site appeared as a tiny, polypoid structure approximately 1.0 mm. in diameter. On the tip of the polyp was a hemorrhagic mass 4.0 mm. in diameter, the base of which was extremely vascular. Aside from these features, it did not differ from several other polyps present in the uterus. Whether the ovum implanted in a polyp, or whether the implantation site became polypoid, is difficult to determine. Probably the former occurred, since the endometrium largely surrounds the ovum and the latter is above the general level of the endometrium. At any rate other polyps were present, and it is conceivable than an ovum could attach itself to such a structure.

During the process of dehydration which followed fixation, the hemorrhagic portion became detached from the tip of the implantation site (Fig. 8*A*). The polypoid area now measured 1.07 by 0.8 mm. in diameter and was elevated 1.07 mm. above the endometrial surface.

[2]Owing to the large number of coital dates, as well as the abnormal condition of this specimen, the day of probable fertile coitus cannot be estimated.

The endometrium, characteristic of the mature stage, showed stellate crevices of gland mouths and moderate fine wrinkling of the intervening surface.

Sectioned Specimen.—The ovum (Fig. 8*B*) is a mere trophoblastic shell, and by no means a perfect one. The chorionic cavity is extremely small and shows abortive attempts to form mesoblast and possibly also a Heuser's membrane. There is moderate cytotrophoblast formation, but the syncytiotrophoblast is scanty with excessive dilatation of the lacunae. The maternal blood has begun to clot within the lacunae; this probably represents the initial step in the cutting off of nutriment to the ovum which would eventually have led to its death. The syncytiotrophoblast in contact with endometrium is negligible in amount and shows none of the activity one associates with this tissue. Indeed, it seems largely to have degenerated, resulting in deposition of fibrinoid material. Similar material is deposited in degenerating trophoblast associated with maturation of the placenta and in hydatidiform moles.

The endometrium was characteristic of the twenty-seventh day of the cycle, and showed moderate predecidual development, physiologic leucocytic infiltration, and secretory exhaustion of its glands. In the absence of pregnancy, menstruation would undoubtedly have occurred very soon, and it might even have taken place in spite of the pregnancy, because of the extremely defective condition of the ovum. The predecidua about the ovum is moderately prominent and contains many infiltrating macrophages and a few polymorphonuclear leucocytes.

This specimen is of interest because it gives an insight into the pathogenesis of the largest single group (46 and 48 per cent, respectively, in Hertig's[15, 16] two series) of spontaneously aborted ova, the pathologic or blighted ova, which either contain no embryo, or at most an extremely defective one.

Age of Ovum.—There were 4 recorded coital dates within the estimated ovulation time (days 14 through 20 of the cycle). The actual age of the specimen may be anywhere between 11.5 and 17.5 days, although it is probably in its twelfth day of development.

2. *Slight Hypoplasia of Trophoblast (Tr-7770)*

Low-Power Examination Prior to Section.—The implantation site appeared as a slightly elevated, oval, hemorrhagic ring, 1.07 by 1.35 mm. in diameter (Fig. 9*A*). Its center was translucent but showed finely stippled hemorrhagic areas. After fixation, this appearance was found to be due to the epithelial defect created by the ovum. The surrounding endometrium was congested over a zone approximately 10 mm. in diameter. On the posterior wall, corresponding to the position of the implantation site, was a punched-out area, 2.5 mm. in diameter, with a hemorrhagic margin. This was similar to the hemorrhage opposite the implantation site of the normal 11.5-day stage.

Fig. 8.—A pathologic previllous ovum without embryonic rudiment, Be-7771. *A.* Surface view (under fluid) of the polypoid implantation site. The latter is at the edge of the uterine cavity, the lateral sulcus of which is represented by the diagonal furrow to the left of the ovum. The roughened tissue to the left is the cut surface of the myometrium. ×14.

B. A mid-cross section of this defective ovum showing an empty chorionic sac embedded within a polypoid mass of endometrium that has undergone a moderate decidual reaction. Aside from the obvious defect—the lack of an embryo—the ovum presents a marked deficiency of trophoblastic development. The syncytiotrophoblastic element is very hypoplastic and shows marked dilatation of its lacunae. ×100.

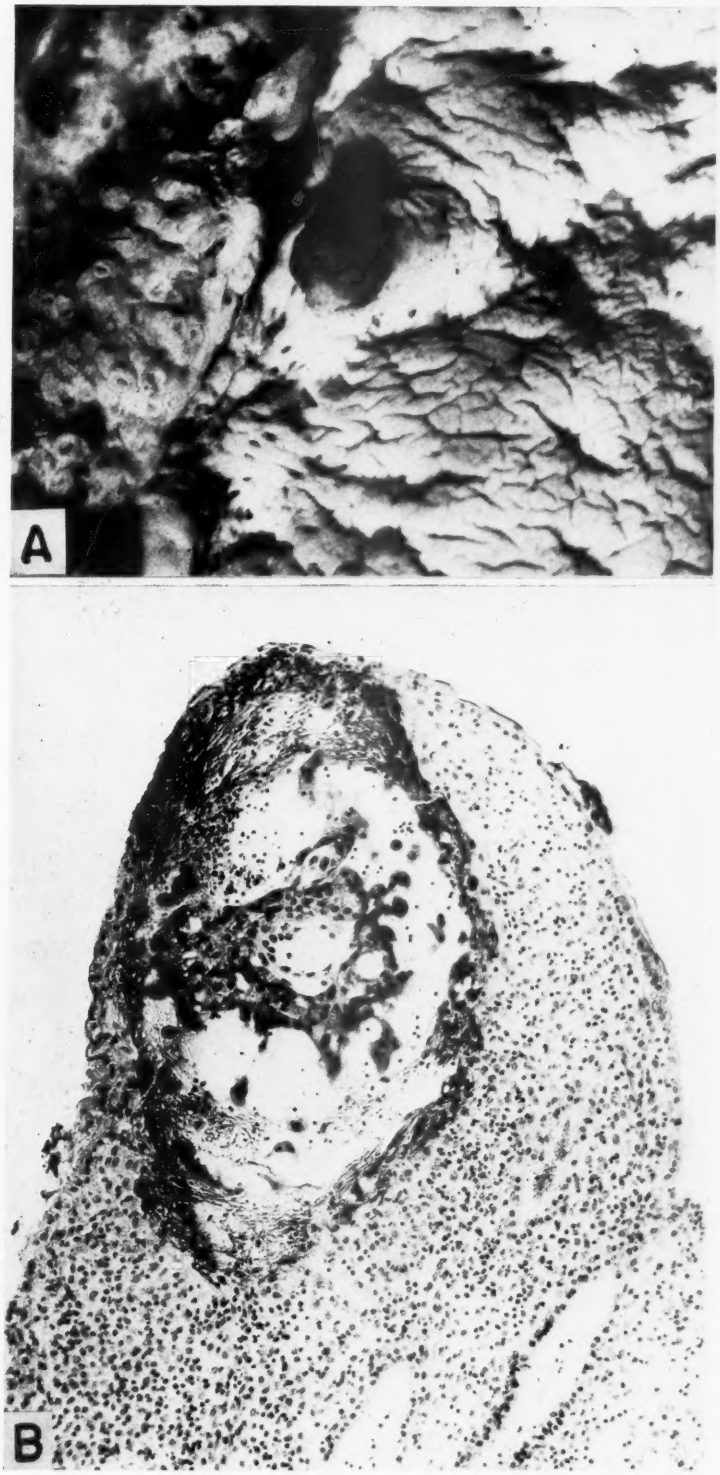

Fig. 8.—For legend see opposite page.

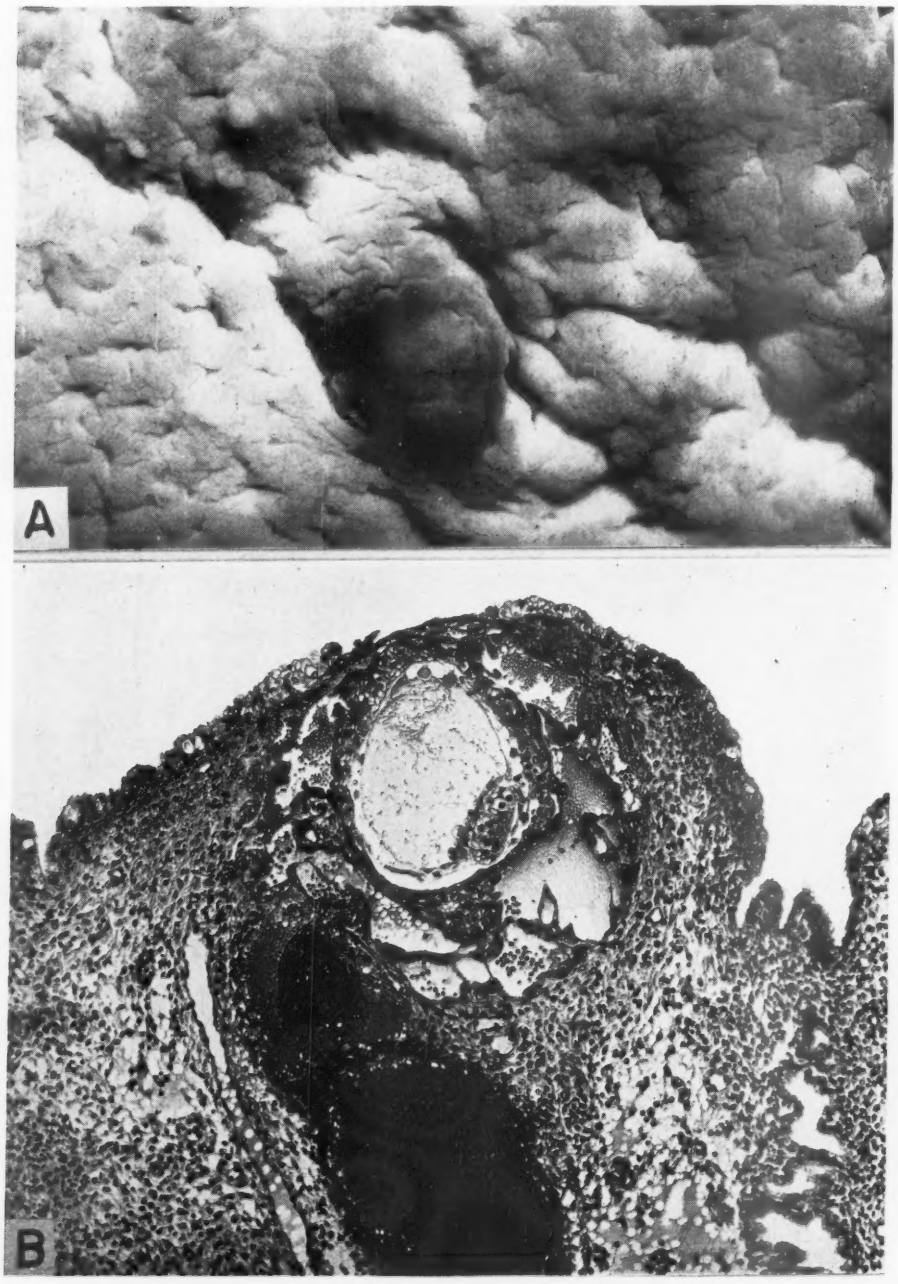

Fig. 9.—A pathologic previllous ovum with slight hypoplasia of the trophoblast, Tr-7770.—*A*. Surface view (under fluid) of implantation site. The hemorrhagic elevation, with the small, oval ulcer in the center, is caused by the implanted ovum. The endometrium resembles early decidua. ×22.

B. A mid-cross section of the ovum and its surrounding endometrium. Although the embryo and the attached exocoelomic membrane are essentially normal, the amount of primitive mesoblast, or connective tissue, lining the chorionic cavity is deficient. The cytotrophoblast is probably within normal limits of development, although the syncytiotrophoblast is moderately hypoplastic. The lacunae are dilated and filled with blood. The hemorrhage below the ovum is within a gland and is not necessarily pathologic, as shown by its occurrence in the normal 13.5-day specimen (Fig. 6*B*). The endometrium is normal. ×100.

Sectioned Specimen.—The ovum itself (Fig. 9*B*) is quite similar to Si-7699, Re-7950, and Al-7700 (Figs. 3*C*, 4*C*, and 5*B*, respectively). However, it is actually smaller than even the youngest of these, although certain features, such as the degree of primordial villous development and of hemorrhage into the trophoblastic lacunae, are quite advanced. The trophoblast appears to be deficient, both relatively and absolutely, particularly with respect to the syncytial element. This deficiency is somewhat reminiscent of the previous specimen, Be-7771 (Fig. 8*B*), although not to such a marked degree.

The relative lack of primitive mesoblastic development within the chorionic cavity is also in keeping with the hypoplasia of the trophoblast, since the latter gives rise to this future chorionic connective tissue. Within the exocoelom there is some deposition of fibrin, the source of which is not evident.

Embryo.—The embryo is not remarkable except for its somewhat eccentric position, a feature observed in 2 of the normal specimens, Si-7699 and Ru-7801 (Figs. 3*C* and 6*B*).

The endometrium, typical of the twenty-fifth day of the cycle, showed saw-toothed, secreting glands, moderate predecidual reaction, and some dilatation of the vessels. In the neighborhood of the ovum, edema was fairly prominent, with early predecidual reaction, some recent hemorrhage, and slight leucocytic response. Vascular sinusoids were fairly prominent but often devoid of erythrocytes. Hemorrhage has occurred into an eroded gland similar to that seen in Fig. 6*B*. The endometrial epithelium is defective over approximately one-half the implantation site with consequent direct exposure of the underlying trophoblast.

Age of Ovum.—The probable fertile coitus took place on the eighteenth day of the cycle, 12.5 days prior to operation. An additional coital date recorded on the twenty-seventh day of the cycle is most likely not significant. The assigned developmental age of approximately 11.5 days is in keeping with the clinical history, as well as with the similarity of this conceptus to the 3 normal specimens of this general age group.

3. *Hypoplasia of Trophoblast (Er-7850)*

Low-Power Examination Prior to Section.—In the fresh specimen, the implantation site appeared as a crescent-shaped, hemorrhagic area, approximately 1.0 mm. in diameter, surrounded by a tiny, pearl-gray elevation which showed slight congestion or hemorrhage.

After fixation, the implantation site measured 1.44 by 1.62 mm. and was elevated 0.35 mm. above the endometrium (Fig. 10*A*). The "Schlusscoagulum," with its characteristic mottled hemorrhagic appearance, was plainly visible, as was also the crescent-shaped area of hemorrhage; the latter, seen previously in the fresh specimen, was due to blood in the trophoblastic lacunae.

Sectioned Specimen.—The most prominent feature of this pathologic ovum is the extreme dilatation and congestion of the trophoblastic lacunae (Fig. 10*B*). The syncytiotrophoblast is very hypoplastic, its substance being reduced to a relatively few tiny, irregular strands lying between the hypoplastic chorionic membrane and the thin peripheral shell of degenerated syncytiotrophoblast. Curiously enough, the best cytotrophoblastic development, as well as the correlated mesoblast formation, is seen on the abembryonic pole where the maternal blood supply is least abundant. The lacunae are directly continuous

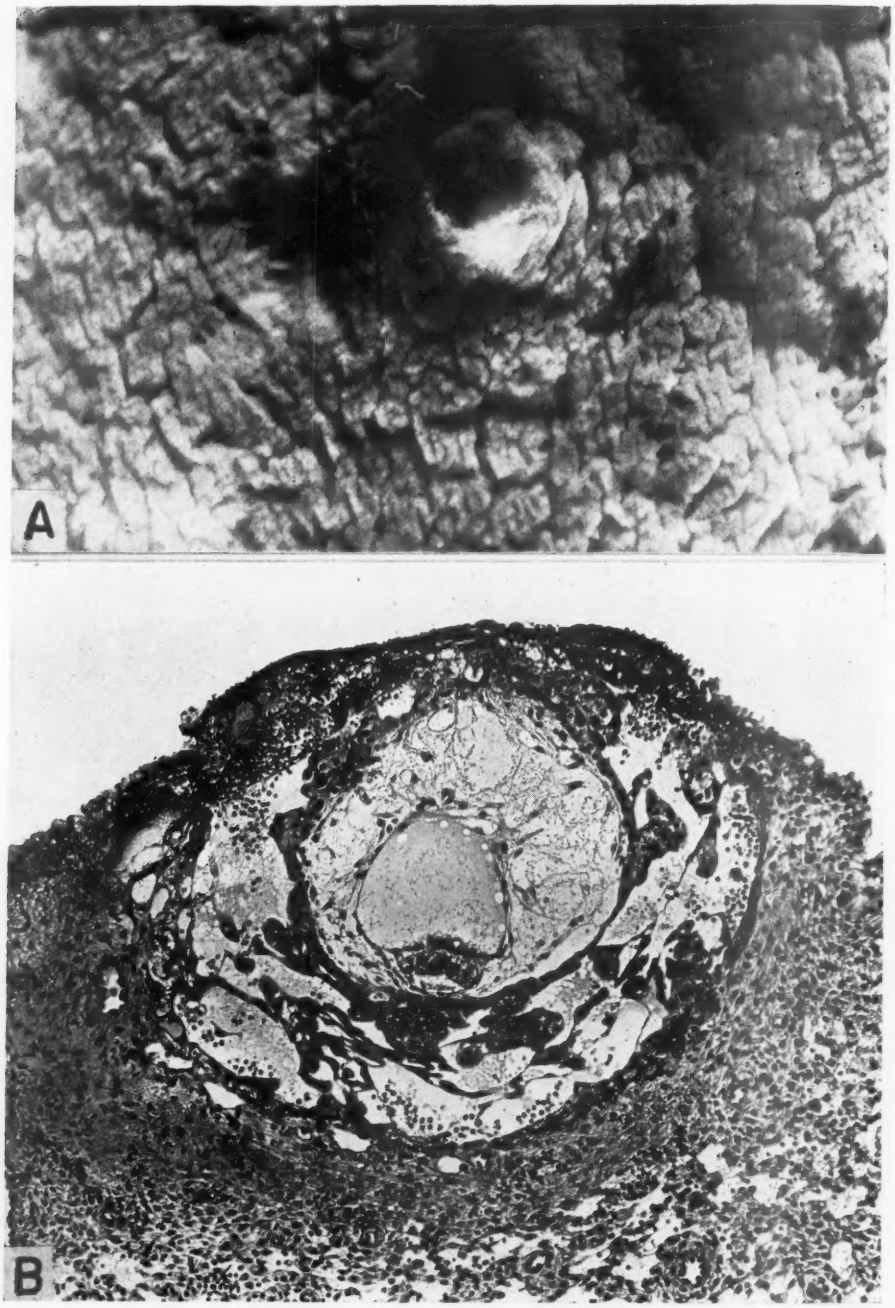

Fig. 10.—A pathologic previllous ovum with slight hypoplasia of the trophoblast, Er-7850. *A*. Surface view (under fluid) of implantation site. The latter is represented by the hemorrhagic elevation just above the center of the photograph. Partially surrounding the ovum is the crescentic area of hemorrhagic and congested endometrium.

B. A mid-cross section of the ovum and surrounding endometrium. The latter shows early decidual reaction. The syncytiotrophoblast is deficient in development and shows accentuation of lacunae containing more blood than usual for this stage of development. The embryo is essentially normal. ×100.

with the "Schlusscoagulum," and the blood within these spaces has undoubtedly contributed largely to its formation.

The endometrium adjacent to the ovum shows a definite decidual reaction with pronounced leucocytic infiltration. There is moderate vascularity in response to the presence of the ovum, although, in keeping with this general stage of ovular development, the dilated sinusoids contain relatively little blood. Elsewhere, the endometrium is of the late secretory type with an early decidual reaction. There is some edema of the stroma and the vessels are large and congested.

Embryo.—The embryo is not particularly remarkable. It possesses a bilaminar germ disc, an amnion and a well-defined exocoelomic membrane. It is slightly smaller than its pathologic contemporary (Fig. 9*B*), and definitely smaller than any of the 3 normal embryos of a similar stage of development.

Age of Ovum.—Since this specimen most nearly resembles the normal 12-day ovum (Re-7950), fertile coitus probably took place on the eighteenth day of the cycle, 12.5 days prior to operation. While coitus was also recorded on the fifteenth and twenty-first days, it seems unlikely that conception occurred on either of these occasions.

4. *A Shallowly Implanted Ovum (Sm-8000)*

Low-Power Examination Prior to Section.—The only evidence of the presence of this ovum was a 2.7 mm. bright red hemorrhagic mass of polypoid shape (Fig. 11*A*).

The endometrium, after fixation, was characteristic of the late secretory phase; the surface was finely wrinkled with only slightly prominent stellate crevices made by the mouths of the glands.

Sectioned Specimen.—The striking feature of this ovum is the shallowness of its implantation (Figs. 11*B* and 11*C*). While the trophoblast is fairly normal for the eleventh day of development, one-half of the ovum projects above the endometrial surface and is covered only by the hemorrhage seen in the fresh specimen. As in the previous conceptus (Er-7850), which likewise is imperfectly implanted for its age, the hemorrhagic cap is continuous with the lacunar spaces from which the blood has escaped.

The embryo is not remarkable for this stage of development, nor is the maternal reaction to the conceptus unusual. Here, therefore, is an example of an apparently normal ovum which has become poorly implanted and would probably have aborted in the not too distant future. If abortion did not occur, it is conceivable that such an ovum might lead to the formation of a circumvallate placenta, a condition apparently associated with shallow implantation of an otherwise normal conceptus.

Age of Ovum.—The only possible fertile coitus had taken place on the sixteenth day of the cycle, 11.5 days prior to operation. The specimen was accordingly estimated to be 11 to 12 days old.

5. *Extreme Hypoplasia of the Trophoblast (Br-7800)*

Low-Power Examination Prior to Section.—Evidence for the presence of an implanted ovum was seen in a small hemorrhagic elevation 3.78 by 3.42 mm. (Figs. 12*A* and *B*). Beneath and to one side of the hemorrhagic portion was a translucent elevated area, 3.0 by 2.7 mm., containing a rounded, bluish spot, 0.7 mm. in diameter. The raised zone represented the ovum, and the bluish spot—the hemorrhage into a gland beneath the ovum (Fig. 12*C*).

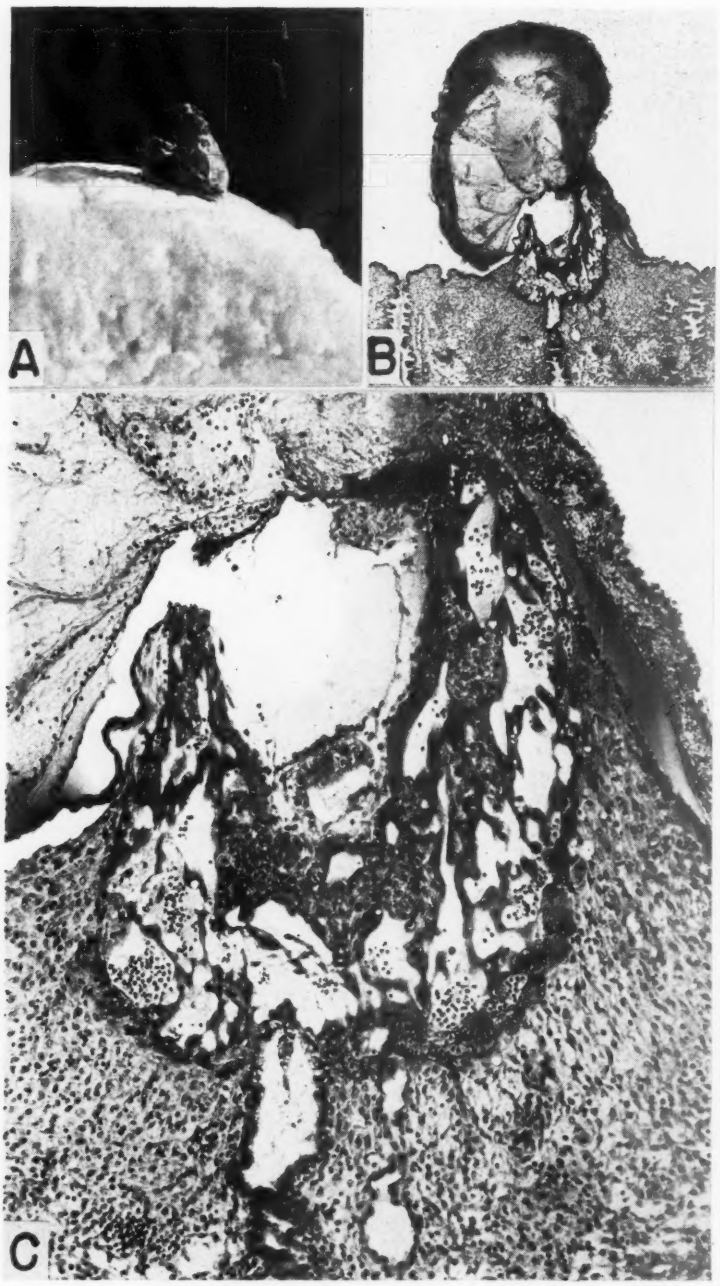

Fig. 11.—A shallowly implanted but otherwise normal ovum, Sm-8000. *A*. Lateral view of block of endometrium containing the implanting ovum. Note hemorrhage above the implantation site. ×5.

B. Low-power view of mid-cross section of implantation site to show the degree to which the ovum protrudes above the surrounding surface. The blood clot occupies the position of the usual operculum. ×20.

C. A detailed view of ovum (same section as Fig. 11*B*). The essentially normal features of the ovum are evident. The break in the abembryonic pole of the ovum is probably a traumatic artefact. For this stage of development (ca. 12 days), the ovum should be well embedded. ×100.

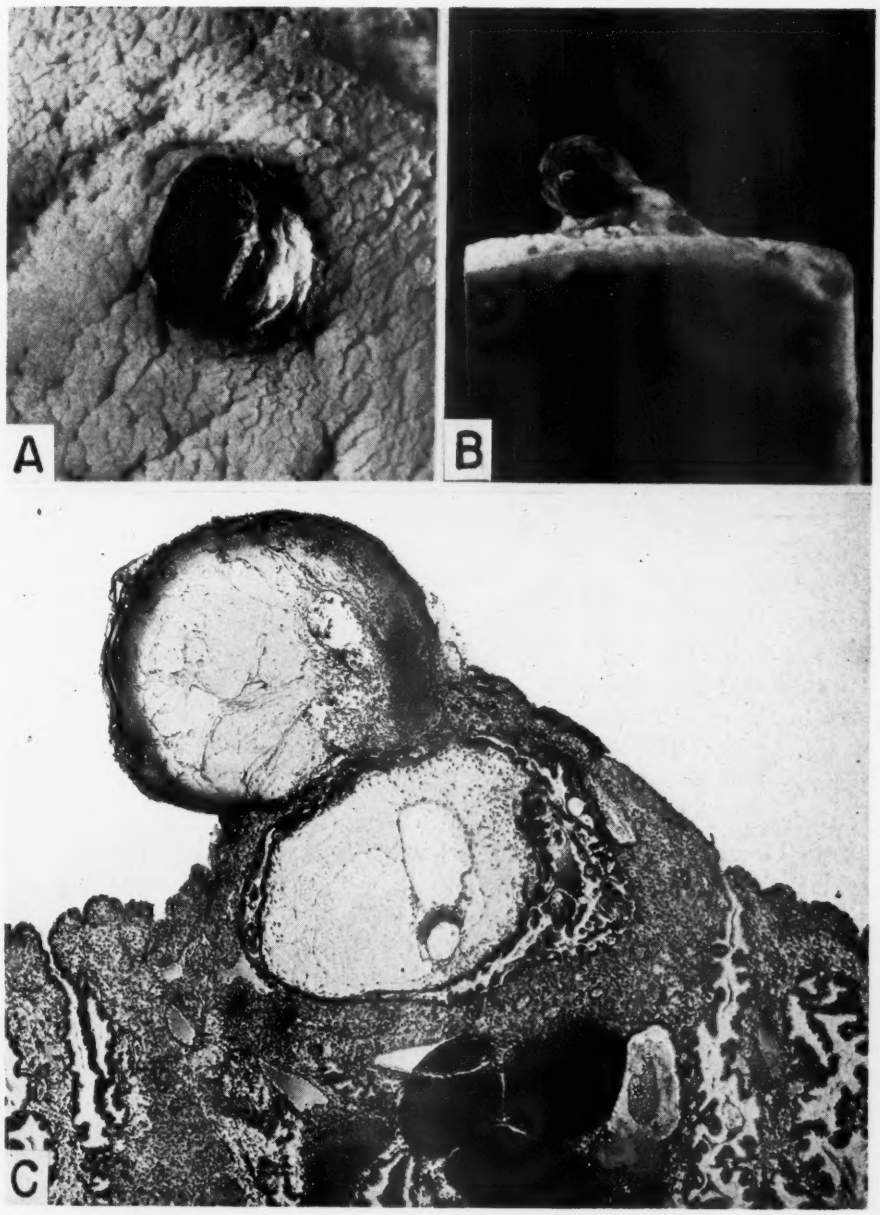

Fig. 12.—A supposedly early villous ovum with extreme hypoplasia of the trophoblast, Br.-7800. *A.* Surface view (under fluid) of implantation site. The most prominent feature is a hemorrhagic mass on top of, and to a large extent replacing, the operculum. ×8.

B. Implantation site, lateral view, showing the hemorrhage on top of elevation made by implanting ovum. ×8.

C. A mid-cross section of the ovum and surrounding endometrium. The most striking feature in this specimen is the extreme hypoplasia of the trophoblast around three-quarters of the periphery and the marked abnormality of the remaining trophoblast. An ovum containing an embryo in this stage of development (well-developed amnion and yolk sac) should be about 13 to 14 days of age. Compare the degree of trophoblastic development of this specimen with that of the normal 13.5-day ovum (Fig. 6*B*). ×35.

Sectioned Specimen.—The principal features of this conceptus are a very deficient trophoblast, but a relatively normal embryonic disc. The exocoelomic membrane has begun to break up and a definitive yolk sac has now formed. Approximately two-thirds of the trophoblastic shell is represented by an indifferent or degenerated syncytium and only a very thin Langhans' layer. The remaining one-third shows abortive attempts at syncytiotrophoblastic formation with lacunae containing maternal blood. No sign of villous formation is present, in spite of the fact that the degree of embryonic development indicates that there should be numerous simple villi at this stage (Figs. 6*B* and 7*B*).

The remainder of the implantation site shows an excellent vascular and early decidual response. Hence the maternal environment per se does not appear to be abnormal.

It would appear, therefore, that this ovum is definitely defective and that its trophoblast would not long support the growing embryo; hence abortion would probably have occurred in the near future.

Age of Ovum.—There are several recorded coital dates, none of which, however, is critical. On the basis of the degree of development shown by the embryonic disc, the developmental age is approximately 13 to 14 days.

Discussion

Even though the ages of the 5 normal previllous ova encompass a time interval of not more than 5 days, there are still many problems to be elucidated within this particular phase of ovular development, due to the scarcity of material illustrating critical stages. Among the questions that await further investigation, or are worthy of special comment, we may briefly mention the following:

Differentiation of the Trophoblastic Elements.—How the two types of trophoblastic cells differentiate is largely influenced by the manner in which the trophoblast responds to its initial contact with maternal tissue. While the two fundamental types of cells appear to be laid down *de novo,* the possibility of their both arising from an indifferent trophoblast that forms immediately upon implantation cannot be entirely ruled out.

Formation of the Trophoblastic Lacunae.—The time and mode of formation of the trophoblastic lacunae have not been satisfactorily determined by the study of our material. Whereas very early vacuolization of an occasional syncytiotrophoblastic mass does take place, most of the lacunar development occurs during the eighth and ninth days of growth. That the lacunae are at first isolated and then coalesce to form a functional intervillous space is evident from the specimens representing the tenth to the thirteenth days of development. It is probably significant that the new lacunae formed during these stages are associated with trophoblast that is eroding blood vessels, hence allowing blood to enter the isolated lacuna prior to the latter's coalescence with the main lacunar system. This may possibly serve as a protective mechanism to prevent blood from flooding the entire system at once. After the vessel is adequately connected with the isolated

lacuna, blood flow into the embryonic placenta is quite likely controlled by vascular tone.

Nutrition of the Ovum.—It is striking that during the first phase of implantation the trophoblast, and hence the ovum, obtains much of its nourishment from actual ingestion of maternal stroma. This, of course, mechanically facilitates implantation, but it probably is not the only reason for such a process. Even as late as the twelfth and thirteenth days of development there still remain evidences of phagocytosed maternal tissue within the syncytiotrophoblast. It is significant, perhaps, that the most active ingestion of such tissue is prior to the time when the trophoblast is in direct contact with maternal blood.

The So-Called "Placental Sign" in the Human Being.—It is interesting that profound vascular disturbance in the endometrium of the implantation site does not occur until about the twelfth day when one encounters, in this series, congestion and hemorrhage. As students, we were taught that hemorrhage probably took place early, and that this facilitated the nourishment of the ovum prior to the establishment of the uteroplacental circulation.

The presence of blood, or coagulum containing blood, on the surface of the implantation site, is worthy of comment because it brings to mind the so-called "placental sign" in the macaque monkey, first described by Hartman.[17] In the human being, it may conceivably be of practical significance in causing miscalculation of the estimated date of confinement, since it occurs at about the time of the first missed menstrual period. The pregnancy in which such hemorrhage, even though scanty, is noticed by the patient and mistaken for a menstrual period, would appear to be one month shorter than is actually the case.

Repair at the Implantation Site.—The relative degree of epithelial repair of the defect created by the implanting ovum varies among the specimens, and apparently depends upon the depth of implantation for any given degree of ovular development. Thus the reparative process has progressed to the slightest extent in two pathologic ova which are shallowly implanted.

Endometrial and Ovular Development.—The correlation of ovular and endometrial maturity deserves some speculation. On the basis of comparative studies in the macaque, one would expect an 8- or 9-day blastocyst to implant on a 22- or 23-day secretory endometrium, the pattern of which would show relatively little variation in different specimens of this age group. As a sequel to this assumption, one would expect a given stage of ovular development to be associated with a definite corresponding endometrial phase, but such is not always the case. Thus, whereas the 12-day specimen of our series is embedded in 23-day secretory endometrium, the 9.5-day one is associated with 26-day endometrium. There can be only two explanations for such discrepancy: either the ovum implants at a variable stage of its development, or it implants on endometrium that may vary in its degree of secretory development. The

latter may be due to delay in fertilization of the ovum, or to variations in the endometrium itself, on the basis of corpus luteum activity. Probably both factors are concerned in this unexpected picture. Actually in the human being, the single implanted blastocyst available indicates that it can embed at the age of approximately 6 days on 20-day endometrium. The human ovum has also been found to implant as late as the twenty-third day, judging from the 9.5-day specimen, or as early as the eighteenth day, as was the case in the 12-day one. A more extensive series will serve to elucidate this matter.

Location of Embedment.—There was no correlation between the position of the implanted ovum and the side on which the corresponding corpus luteum was found. The ovum may embed anywhere in the uterine cavity, irrespective of the ovary of origin. On the other hand, in our limited series there appears to be a definite correlation between the position of the ovum and its condition: the normal ova were, without exception, recovered from the posterior wall of the uterus, while the abnormal ones embedded on the anterior wall. The importance of this finding is probably more apparent than real, since this series can hardly be statistically significant.

Factors Influencing Condition of Ova.—From a preliminary survey of the pathologic material among our specimens, it is apparent that various types of abnormality are encountered. Most of them appear to be associated with intrinsically defective ova, although shallow implantation seems clearly to play a part in the pathogenesis of these future abortions. Whether the most defective ovum of the group (Be-7771) became abnormal because it implanted on an endometrial polyp, or whether it was intrinsically abnormal, is impossible to determine. It is certain, judging from at least one of the other specimens (Br-7800, Fig. 12) that the endometrial environment cannot invariably be held responsible for the extreme degree of trophoblastic hypoplasia observed.

Summary

A series of 5 previllous and 2 villous normal human ova, ranging from 7.5 to 16.5 days in developmental age, shows that the human blastocyst implants on the posterior wall, probably during the late sixth or nearly seventh day of its development, on endometrium that may range from the eighteenth to the twenty-third day of its development. Actually there are no precise data on the time of implantation, since the youngest specimen, and therefore the most critical one with respect to this process, is already implanted. The figures given (late sixth or early seventh day) are deduced on the basis of this youngest specimen. Even younger ova must be secured in order to determine the actual time of implantation.

Trophoblast proliferates at the site of implantation which, at first, consists of solid cyto- and syncytiotrophoblast. The latter becomes vacuolated on the eighth day to develop lacunae for the reception of maternal

blood on about the eleventh day. The chorionic villi begin to form as cytotrophoblastic masses on the twelfth to thirteenth day and grow peripherally along the syncytiotrophoblastic framework, ultimately coalescing peripherally to displace the syncytiotrophoblast, except the portion lining the intervillous space. Remnants of the desquamated syncytiotrophoblast are encountered in the placental site as giant cells.

A series of 5 abnormal previllous ova, the developmental ages of which range from approximately the eleventh to the fourteenth day, but which are difficult to interpret accurately because of their abnormality, shows a variety of conditions ranging from shallow implantation of an otherwise normal ovum, through extreme hypoplasia of the trophoblast, to complete absence of the embryonic mass. The pathologic ova were all found on the anterior wall of the uterus.

A. Conclusions.—Normal Ova

1. A series of normal previllous human ova, discovered in uteri removed surgically prior to the first missed menstrual period, is reported.

2. The human blastocyst probably implants during the late sixth or early seventh day of its development on endometrium that may show the characteristics of the eighteenth to the twenty-third day of development.

3. The solid syncytiotrophoblast of the early implanted blastocyst develops lacunae, beginning on the eighth day, which subsequently coalesce and begin to receive maternal blood on about the eleventh day.

4. Chorionic villi form from peripherally growing masses of cytotrophoblast which arise from the chorionic membrane on about the twelfth day.

5. The peripheral syncytiotrophoblastic shell of the previllous ovum is "desquamated" at approximately the same time as the cytotrophoblast of primitive villi makes contact with the decidua.

6. The "placental site giant cells" are the remnants of this desquamated syncytiotrophoblast.

B. Conclusions.—Abnormal Ova

1. Five pathologic or pathologically implanted previllous ova, discovered in uteri removed surgically prior to the first menstrual period, are reported.

2. Shallow embedment of one ovum apparently accounts for the abnormality encountered in an otherwise normal nidation site.

3. Varying degrees of trophoblastic hypoplasia are observed in 4 intrinsically pathologic ova.

4. Absence of the embryonic rudiment is seen in an ovum showing faulty trophoblastic development and apparently implanted on an endometrial polyp.

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THE BLOOD VESSELS OF THE MYOMATOUS UTERUS

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IN 1912 John A. Sampson[1] published a paper about the blood supply of uterine myomas. There is no other similar study of the subject in the English language. This fact, if there were no others, would seem to warrant a review of the matter.

The blood supply of myomas is obviously related to some of their degenerations; to the reasons why some myomatous uteri bleed while others do not; and finally there are interesting questions to be answered by one familiar with Sampson's work as to the nature of the circulation of the individual tumor. For example, in general, he found each myoma a mass of proliferating arteries and in most instances could demonstrate few if any veins within the tumor substance. Sampson never believed this to be an injection fault and his opinion is apparently correct. Therefore, the mechanics of arteriovenous exchange in myomas is perhaps capable of clearer visualization than in his work. In a personal letter last year, also, Sampson kindly expressed another problem to be checked: namely, whether in his injections—since he did not measure injection pressure he might have overinjected the arteries and perhaps have filled the lymphatics—that being a possibility in this type of anatomical work.

This paper does not propose to answer all of the questions of tumor degenerations and uterine bleeding but is the presentation of anatomical material obtained by the use of an injection medium new for this purpose, which allows the direct study of the blood vessels of the uterus and the myoma.

Sampson's work, as well as that of Bardon[2] in France, and Holmgren[3] in Stockholm, was done by injection of the myomatous uterus with colored gelatin, the pigment being either plain or radiopaque. Cross slices of the specimens were studied and stereoscopic radiographs made of some cross slices injected with radiopaque material. An accurate picture of the circulation was thereby obtained in most instances from these preparations for, when properly made the blood vessels stood out plainly in the radiograph against the faint background of the specimen. However, the composite picture of the blood supply was always obtained indirectly, i.e., from study of stereoscopic radiographs. In the use of this method there were many problems to be worked out as to proper x-ray exposure and in obtaining radiographs from the proper angles to show the vessels, because nobody could tell beforehand except in a general way, where the major vessels were going to be. Many such technical problems were avoided by the present method of study.

There are several anatomical methods available for the direct study of blood vessels, but most are difficult to use or at best result in incomplete injections. Because of some previous experience with synthetic liquid latex, hereafter for brevity called "Neoprene," this substance was used as the injection medium. This material in the original state is a thin, milky fluid which needs only to be filtered to be ready to use. It does not have to be warmed nor does the specimen need to be warmed before injection, or cooled afterwards to set the injection medium. It coagulates instantly in acid which is added to the normal fixative used for the specimen after the injection is complete.

After some trial two proprietary injection compounds of neoprene were chosen for use, one containing red pigment, the other black. The exact pigments in these compounds the manufacturer* would not disclose. However, it is known that the black pigment does not have a granule size of over 2 microns and the red pigment size is not over 0.4 microns. If it is remembered that the average red blood cell is 7 microns in diameter, it is obvious that neither of these pigments should fail to give a thorough injection. However, granule size is not the only consideration in the completeness of an anatomical injection. Surface tension, vessel spasm, and mutual coagulating action of injection compound and tissues enter into the picture. From experience with neoprene, it is clear that under normal conditions it goes over into but not through the capillary bed. This same conclusion was reached by another worker[1] using these compounds in injections of the kidney.

After injection with neoprene the myomatous uterus was either prepared as a corrosion specimen or cleared by the Spalteholz method. One type of anatomical preparation served as a check on the other.

This material lends itself naturally to the preparation of multicolored corrosion specimens. These are specimens in which after injection the flesh is eaten off with acid leaving only the injected cast of the circulation. Such casts cannot be made after injections with gelatin. When properly obtained with neoprene they resemble a multicolored rubber bath sponge. The routine preparation of corrosion specimens would seem to have the disadvantage that microscopic sections are difficult to obtain without defects in the casts. However, all uteri studied by this method, were cut in half after fixation and only half of the specimen was corroded, or suitable further precautions were taken to protect the patient from whom the myoma was removed. The cervix was amputated and sectioned, since it does not inject in a surgical specimen, and sections were made of any suspicious tumors or suspicious areas in the uterine cavity. The corrosion preparations were uniformly made by injecting the arteries with red neoprene and the veins with black.

Neoprene will tolerate the Spalteholz clearing process which, using slices of a gross specimen, is roughly similar to preparation of a micro-

*American Anode, Inc., Akron, Ohio.

scopic section. After injection the tumor is dehydrated in successive alcohols and then cleared in benzol and wintergreen oil. However, it was found that only the black pigment would stand this process without diffusion. Also it was learned very early that both arteries and veins could not be injected for study in the cleared specimen because of the resulting confusion caused by the heavy black injection. For simplicity, also, only uteri containing single or at the most two or three myomas were studied by this method.

The clearing process when properly carried out, though quite time consuming, results in excellent specimens for study of the arterial system.

Injection Methods

When utilizing surgical specimens it was found necessary, as a rule, to use those removed personally so that proper pedicles would remain for cannulation and undue injury to the tumor avoided during operation. Small glass cannulas (Fig. 3) were inserted into both uterine arteries and veins of the freshly removed specimen and at low pressure the blood washed out by connection to the arterial cannulas. There is a great differences of practice among anatomists in this detail. Washing may be done briefly, not at all, or thoroughly. With this injection medium the most satisfactory injections were obtained after washing the specimen thoroughly with cold tap water for an hour or two, even at the expense of some edema. Thorough blanching of the specimen was thereby obtained. The uterus was then covered and put in the refrigerator overnight and the injection done the next day, there being at this time almost complete disappearance of the edema. During the washing all gross vessels which leaked were ligated. It was found that injection was more difficult if performed later than twenty-four hours for the reason that leaking points previously tied off usually let go, probably from softening of the suture material.

The neoprene injection compound after filtering was introduced into the vessels from a simple pressure bottle to which was connected a mercury manometer. The pressure used never exceeded 180 mm. of mercury for arteries, and 120 mm. of mercury for veins. The end point of injection for arteries was an easy matter because the arterial system filled promptly and the end point could be determined visually, the injection being complete when vessels distant from the point of injection were full. The venous injection was considerably slower and completeness often required some gentle massage of the uterus. When the veins properly filled the uterus turned black, the color of the injection mass, and wherever there was uterine muscle the specimen was slightly swollen and tense. The sensation of filling the venous sinuses of the uterus was that of slowly filling a hot water bottle. During injection small leaks were stopped by sopping with an alcohol sponge.

After injection of one or both circulations, the uterus was placed at once in 5 per cent formaldehyde strongly acidified with acetic acid. When thoroughly fixed, depending on the size of the specimen, from several days to several weeks, it was cut in half usually lengthwise anteroposteriorly and the cut surface of one or both halves was photographed. Tumors to be corroded were then placed in commercial hydrochloric acid in the incubator until digested. Specimens to be cleared were further sliced into thin slices not quite completing the cuts and started through the dehydrating alcohols.

The Blood Vessels of the Normal Uterus

The arteries of the normal uterus follow a fairly constant and definite pattern (Figs. 1 and 2). The course of the uterine artery along each side of the uterus and its free anastomosis with the ovarian artery on the same side is well known. It is also well known that one uterine artery anastomoses freely with the other It is interesting in these specimens that the ovarian artery usually comes off about halfway up unless distorted by the presence of a myoma. From the uteroovarian anastomosis a large branch of the uterine artery usually goes on over the fundus. The fundal branch however is not always an exact continuation of the uterine (Fig. 1). From each uterine artery low down numerous cervical branches course downward but in surgical specimens they are lost by stripping off during operation. From the level of the internal os each uterine artery gives rise to short branches which arch around and penetrate the front or back of the uterus and to these the term "arcuate" has been given. They lie between the outer and middle third of the uterine wall either front or back. They branch at once into many branches which course over the outside of the uterus, and anastomose freely with similar branches from the opposite uterine artery. It is through this peripheral anastomosis that free communication from one artery to the other takes place. From the arcuate arteries, also, and all pointing toward the uterine cavity, the tortuous radial arteries arise. These branch near their bases but terminally end up toward the endometrium (Fig. 2).

In corrosion specimens there is always a small arteriolar tuft on the end of each radial artery which points toward the endometrium. These vessels are at present not considered to be the spiral arterioles of the endometrium itself, because it is uncertain that the injection mass enters them regularly. They are not visible in cleared specimens.

The uterine veins apparently contain no valves and may be easily injected. As said before the venous supply of the uterus is rich. The uterus during injection turns completely black from the pigment in the neoprene and the process of venous injection reminds one of filling a hot water bottle. A rich plexus in the endometrium, which usually fills, is fed by the terminal branches of the radial arteries and communicates with the large and rich plexus in the myometrium. There is a zone of myometrium about the uterine cavity which is relatively anemic venously and appears on the cut surface of all gross specimens (Figs. 8 and 11). About the periphery of the myometrium there are collecting veins, usually accompanying the arcuate arteries, which convey the venous blood of the uterus to the uterine veins overlying the uterine arteries in the broad ligament.

It is needless to say that aside from the variations in the uterine blood vessels produced by myomas they naturally vary with the age of the patient and with the phase of the menstrual cycle. This is especially true of the veins. It is the rule in the woman who is near a menstrual period, or bleeding, to find the endometrium well injected venously and the injection mass even in the uterine cavity (Fig. 8).

The Blood Vessels of Myomas

In corrosion specimens the direct observation of the blood vessels of the uterus and its contained myomas is easy. The black venous injection mass is so heavy that the general contour of the specimen is retained

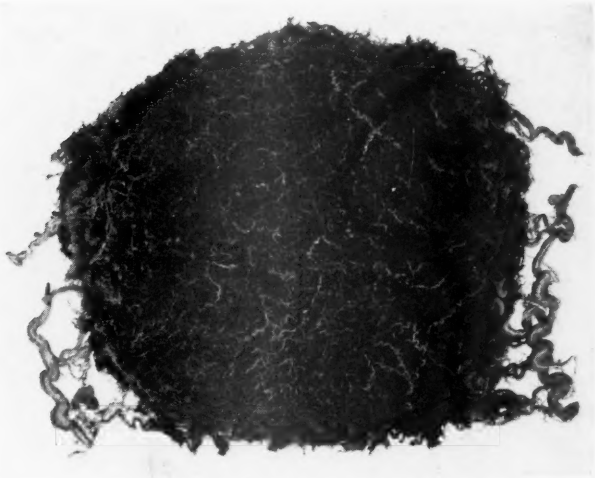

Fig. 1.—Corrosion cast of uterus showing black venous mass and uterine arteries with arcuate branches. Uterine veins cut away. Fundal branch toward top on either side.

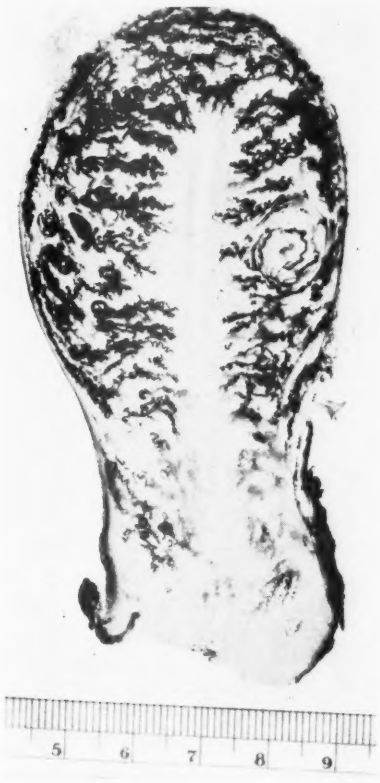

Fig. 2.—Arterial pattern of uterus. Spalteholz cleared preparation. One small myoma in uterine wall. Cervix does not inject in a surgical specimen.

and from this elastic sponge the red arteries may be dissected out if desired. The actual myoma is usually a mass of branching arteries containing few or no veins The veins are usually concentrated about the periphery of the tumor, and enter it only a short distance or not at all. The arterial mass of vessels may be rolled out of its bed in the corrosion preparation and remain attached to the uterus only by its feeding radicals.

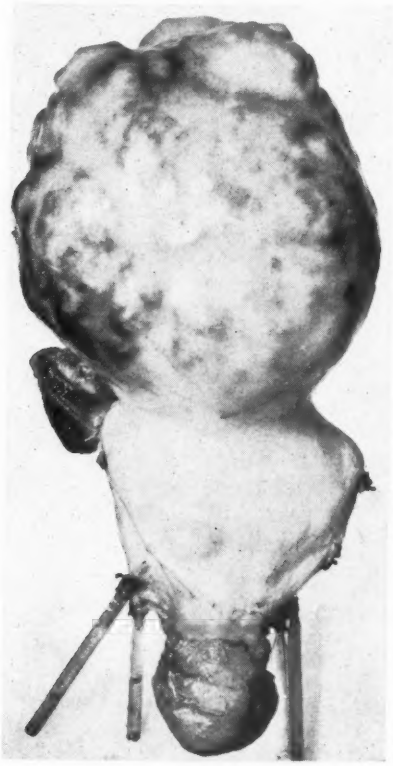

Fig. 3.—Specimen ready to inject. Long cannulas are in uterine veins. Small mass under myoma is an ovary.

From the injections of many different tumors it is obvious, as is well known, that myomas vary greatly in vascularity. In some the mass of arteries will be almost as large as the tumor itself, in others the cast will be much smaller. Holmgren's idea that white compact myomas have fewer vessels is not borne out in this study. As far as the degree of arterial proliferation is concerned no definite rules can be made but, there is the impression that some pink myomas especially those of coarser texture are apt to contain a few veins and show less arterial proliferation. This is logical in that less arterial proliferation is necessary to reach the venous circulation. Larger tumors seem more vascular but probably have no more vessels actually, the mass being larger because of proliferation necessary to keep pace with growth of the tumor.

In any myoma the arteries are coarse as they enter the tumor and branch over its surface. When an individual vessel in a myoma is teased out it is found to be very arborescent, some branches entering the substance of the tumor for quite a distance and others not so far. There

are branches connecting with other vessels approaching from other portions of the tumor. Each branched artery at the end of its finer radicals in the substance of the myoma presents a fine tuft of vessels similar to those at the end of the radial arteries in the uterus. Under the microscope these tufts seem to be arterioles. As separate vessels they are not visible to the naked eye in the corrosion specimen and certainly do not appear in x-ray plates or in the Spalteholz cleared specimen. The presence of these tufts suggests that there is a capillary bed in the myoma which, from the position of the veins, must drain toward the periphery of the tumor to empty into the venous system. Therefore, from study of corrosion specimens it would seem that ordinary arteriovenous exchange in a myoma is through the medium of a capillary bed. No evidence from dissection of the casts was ever found that the same artery could carry blood in and out of a myoma. There is also no evidence at present that injection fills lymphatics.

Fig. 4.—Corrosion cast of specimen in Fig. 3. Venous mass dissected away to show large tortuous arteries of right uteroovarian anastomosis with arc over fundus to left ovarian artery. Left uterine artery very small. Myoma is a mass of proliferated arteries. Most of veins over the myoma have been removed.

Although the uterus is a mass of veins and is almost correctly spoken of as the "venous heart" of the pelvis very few veins as a rule penetrate very far into the myoma itself. Myomas of coarse texture or, as stated above some pink myomas, occasionally show a scant venous injection of their substance. There is every evidence to indicate that the failure to inject the veins in a myoma is not the fault of the medium or method.

Fig. 5.—Veins over the surface of a pedunculated myoma forcibly injected. Spalteholz cleared specimen. No veins penetrated the tumor more than 2 cm. Solid black injection below is a portion of the uterus.

Fig. 6.—Spalteholz cleared specimen. Large myoma to left 9 cm. in length had only one nutrient artery. Degeneration. Other smaller myomas in uterus had better blood supply.

Every device was employed to force the venous injection mass into any veins that might be in the substance of the tumor. In one instance (Fig. 5), the pedicle of a pedunculated myoma and the veins over its surface were thoroughly "milked" and still no venous material went very far below the surface. There is certainly never a venous supply in a myoma approaching the richness of that in the myometrium.

As is well known, the arteries and veins of the uterus containing fibroids are frequently much increased in size, especially in larger tumors. One is struck with the fact that in a uterus containing many myomas there may be a division of labor, so to speak, between the uter-

Fig. 7.—Arteries around a submucous myoma under endometrium. Spalteholz cleared specimen. This myoma received branches at opposite poles from each uterine artery.

ine vessels, one artery feeding some of the tumors, the other uterine running to the others (Figs. 8, 9 and 10). In the case of many intramural tumors of good size there are branches to the tumor from a vascular arc in the uterus contributed to by one uterine and both ovarian vessels. The other uterine vessel may be very small by comparison (Fig. 4). Anastomotic branches from one side of the uterus to the other may become quite large and conspicuous.

Intramural myomas of any size are very rarely found without three or four nutrient vessels entering its substance. The vessels are all branches of a vascular arc in the uterus and usually enter the tumor at opposite poles. It is quite clear that any myoma of larger size which has only one nutrient vessel is to be considered undernourished and may al-

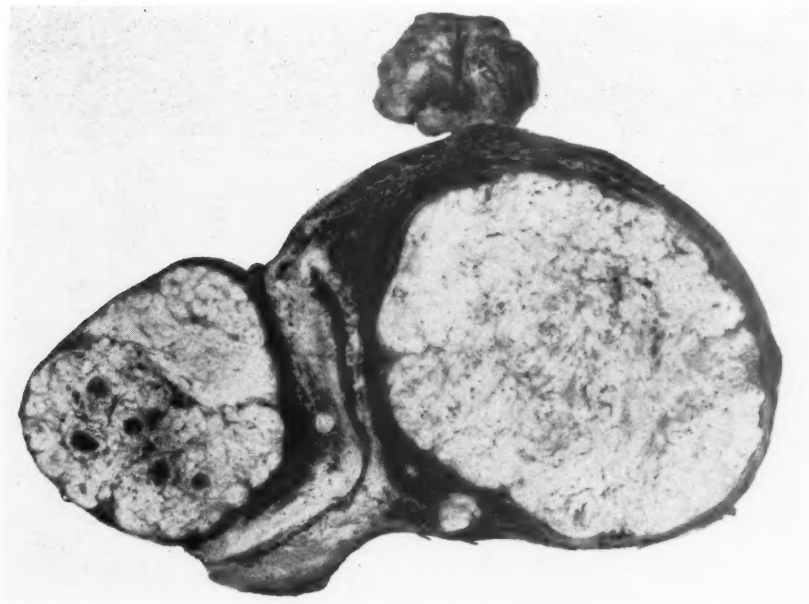

Fig. 8.—Myomas in uterus removed during menstruation. Largest myoma 8 cm. in diameter. Black venous mass in uterine cavity. Occasional veins injected in larger tumor with mass of proliferated arteries smaller than normal. Tumor to left is compound myoma with veins between nodules, two of which show small areas of degeneration.

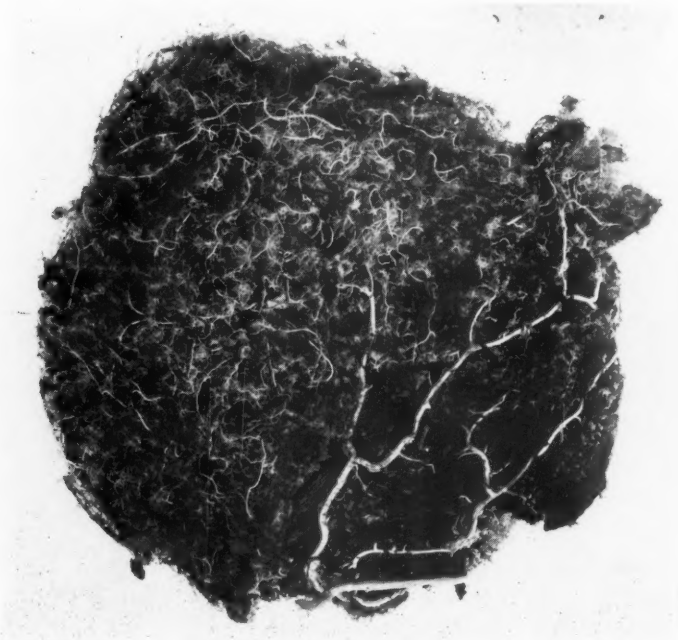

Fig. 9.—Posterior view of specimen in Fig. 8. Veins partly removed. No branches to large tumor. Large ones to smaller compound myoma (bottom of picture). Pedunculated tumor split open to show internal arterial mass proliferated from two feeder arteries.

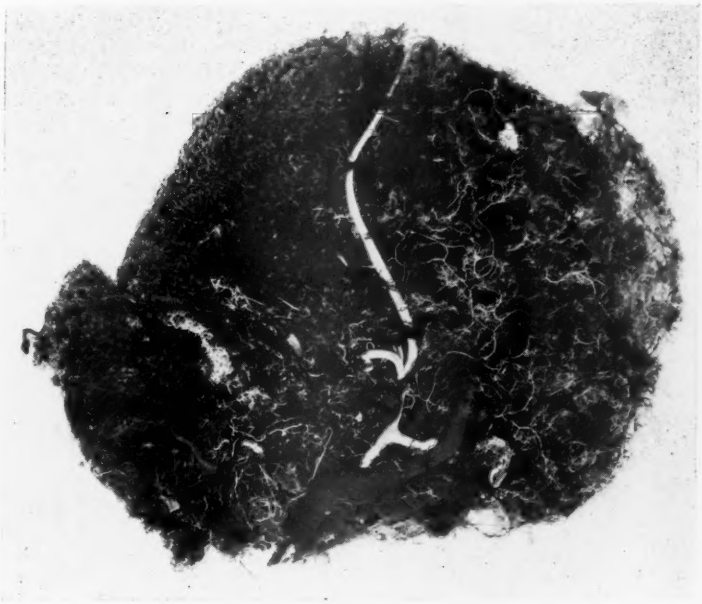

Fig. 10.—Outside of other half of specimen in Fig. 8. Shows the veins to the large tumor. Uterine cavity split open at left.

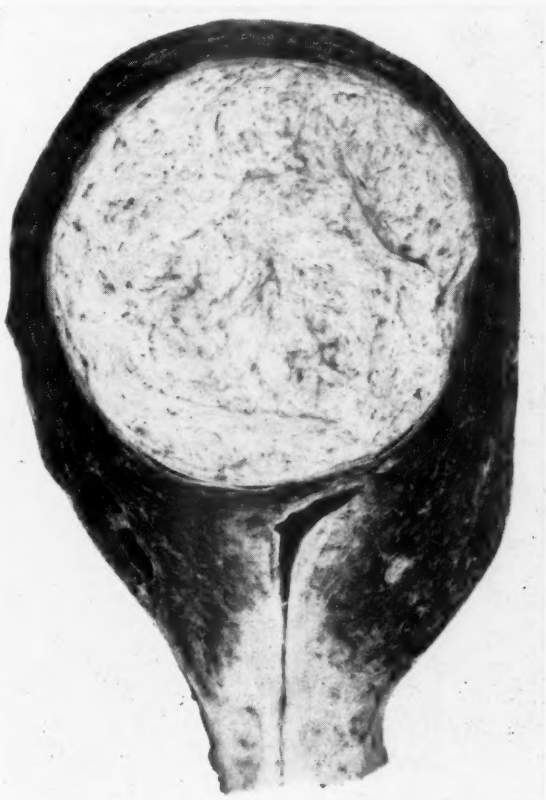

Fig. 11.—Compact intramural myoma. No veins could be injected in this tumor.

ready show signs of degentration (Fig. 6). In very small myomas it may be difficult to tell whether there are multiple nutrient vessels or not. Frequently the substance of the tumor seems to be fed by the arborescent proliferation of one small artery, but there is no reason why neighboring arteries in the myometrium might not be sending in small short branches. As stated above, it is very plain that this happens in larger tumors. (Figs. 11, 12, 13.)

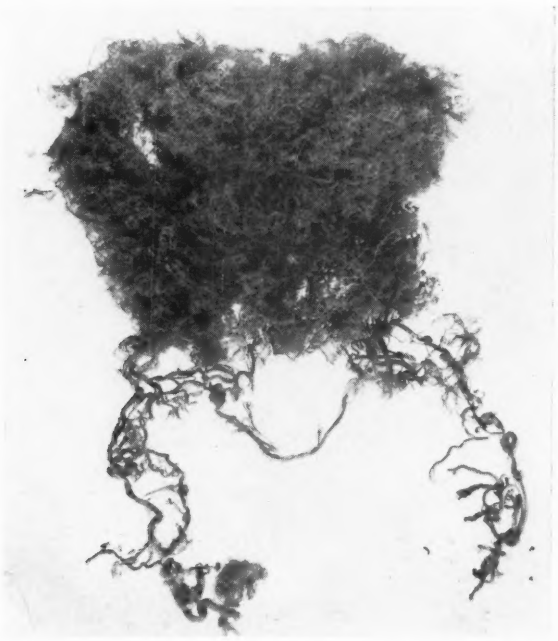

Fig. 12.—Major arteries dissected from cast of entire specimen in Fig. 11. Near lower end of right uterine artery is the arterial mass of a small myoma.

It is probably true that the correct picture of the blood vessels of a myoma cannot be obtained from the study of pedunculated nodules. As the myoma is extruded from the uterus some of the branches feeding it may become of secondary importance and on occasion there may finally appear to be only one nutrient artery. Such a tumor degenerates unless it acquires collateral vessels from an adjacent structure such as omentum, etc. As a rule in subserous and pedunculated myomas that show no degeneration or parasitism, the pedicle or base is made up of many arterial branches from the aforesaid arc in the uterus, the only change from the intramural position being that their polarity is disturbed: viz., the vessels now enter the capsule of the tumor all at one point. The same is true of well pedunculated submucous myomas, but in submucous myomas still fairly well embedded in the wall of the uterus, it has been observed that nutrient vessels still enter the tumor from the myometrium at opposite poles.

Similar to Sampson's observations no good venous injections have been obtained of the endometrium over the projecting surface of a submucous myoma. The arteries over the surface of the tumor are intact and under the endometrium in the capsule of the tumor (Fig. 7). Therefore, with relative anemia over a submucous myoma, it is evident that unless ulcerated, the uterine bleeding frequently accompanying such

Fig. 13.—The blood vessels of the myomatous uterus. Corrosion cast of the half specimen of Fig. 11. Red arterial mass of myoma rolled up out of its bed showing the nutrient vessels. Radial arteries project toward uterine cavity below. This picture shows very well the nature of the corrosion preparation.

tumors does not come from the tumor itself, but is, when present, from the endometrium near-by which sometimes injects heavily with the venous mass. The endometrium may be normal or abnormal histologically but it seems logical to conclude that the bleeding may be contributed to by poor contracting power of the uterus due to the presence of the tumor.

Mention must be made of some myomas which on injection show admixture of arterial and venous injection masses. No absolute statement to cover all cases can be made as to the cause of this abnormality of injection but there is the impression that it is usually due to injury of the specimen during its removal. With the rich venous bed of the uterus and the large veins about the periphery of myomas, it is not surprising that the venous system might easily fill with any arterial mass set free anywhere within the specimen. This is what usually happened although occasionally the venous injection mass also seemed to flow back into the arteries. These specimens are rare and further study of them is being made to form some conclusion as to the presence or absence of actual arteriovenous fistulas in myomas. If free communications exist a revival of some of the older ideas about myoma heart might be in order. Four such specimens in the first sixty studied were encountered and injury was proved in both of two smaller ones. In two larger specimens injury was not found and the specimens were discarded.

Summary

Employing anatomical methods which allow the direct inspection of the blood supply of the myomatous uterus, the distortions in the blood vessels of the uterus caused by these tumors and the intrinsic vessels of the tumors themselves were studied. The fact that most myomas are a mass of proliferating arteries and contain few or no veins within their substance is confirmed. No normal myoma has only one nutrient artery. The frequent arteriolar tufts seen in corrosion specimens are pointed out as evidence that a rich capillary bed probably exists, emptying toward the periphery of the tumor. No evidence of blood entering and leaving a myoma by arterial channels was found. Free arteriovenous anastomoses were encountered four times in sixty specimens but probably were tumors injured at operation. Even overinjection of arteries does not fill lymphatics in or around myomas.

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FALLACIES IN SOFT TISSUE PLACENTOGRAPHY*

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WHEN haemorrhage occurs from the uterus at or near term grave issues may depend on a rapid and accurate determination of the position of the placenta. The diagnosis is usually made by digital palpation, but in a major degree of placenta praevia this examination will sometimes provoke alarming bleeding. For this and other reasons alternative methods of investigation have been sought, and, in particular, much attention has been paid to the possibility of radiological diagnosis. Some success has been achieved by the use of methods that reveal the thickness of tissue separating the foetal head from the bladder wall; radio-opaque substances injected into the amniotic sac have also been used to display the outline of the uterine wall. These methods—especially the first—have a certain usefulness, but they do not concern the purpose of this paper, and will not now be further considered.

In 1934 Snow and Powell[1] claimed that the soft tissues of the pregnant abdomen, including the placenta, could be visualised by "straight" radiography. Further contributions appeared in 1939 by Snow,[2] and by Snow and Rosensohn.[3] In 1940, Dippel and Brown[4-6] reported favourably on the simplicity and reliability of the method, claiming successful identification of the placental site from a single radiograph in 90 per cent of cases. Following these leads, soft-tissue placentography has been put to considerable test in the Nuffield Department of Obstetrics and Gynaecology at Oxford. At first a favourable impression was formed, but with increasing experience it was found that the interpretation of the x-ray films was open to serious error. The conclusion has now been reached that, in the form originally described, the method may lead to grave mistakes in diagnosis.

Method

In a good radiograph it is usually possible to trace the outline of the wall of the pregnant uterus for a considerable part of its circumference. In the usual anteroposterior picture much of the view is obscured by the maternal skeleton, and for that reason the lateral or profile view is of greater service. In such a radiograph the following structures can be seen: (1) the maternal skin, (2) the muscles of the abdominal wall, (3) the wall of the uterus, (4) the surface of the foetus and (5) the deeper structures of the foetus.

*Contributions from foreign sources are not accepted as a general rule for publication in the JOURNAL. However, this particular article bears a close relation to similar research in this country and the appended rebuttal is made by an American author. The English spelling has been retained.—*Editor.*

There is an extreme range of density in the radiograph between the heavily exposed anterior portion, and underexposed posterior portion. If, however, the picture is viewed by an illuminant that can be varied from dimness to extreme brilliance, much of the difficulty caused by uneven density is overcome. It is also a considerable advantage to reduce the time of development of the films to one-third of normal. Experiments have been made with various forms of differential filters to secure an evener film exposure. Although improved results have been obtained, I agree with Dippel that the advantages of such devices scarcely compensate for the troubles encountered in their use. In a stout subject it is best to make two pictures: the first is taken with a low voltage to reveal the anterior structures; the second, taken with a much higher voltage, displays the thick posterior structures. During the second exposure the anterior area should be shielded by a lead sheet placed between the patient and the x-ray tube.

In radiographs so obtained, the uterine profile is clearly seen. Immediately above the pubes the uterine wall is usually sharp in outline and even in thickness. At a higher level a sudden change takes place. While the outer surface continues in even outline, the inner surface abruptly alters, so that the thickness of the uterine wall now appears to be twice, or many times, as great as before; in addition, the outline is usually less sharply defined. Tracing the shadow still further, the wall is again seen to diminish so that it resumes—or nearly resumes—its original thickness. The expansion commonly extends over a quarter or a third of the visible portion of the uterine wall; it oftenest occurs anteriorly, or in the fundus; it rarely occurs in the posterior part of the body. (Figs. 1 and 2.) This thickening is accepted by Snow, Dippel, and their associates to represent the placenta. It is not possible to distinguish placenta from the uterine wall, for, except in rare instances of placental calcification, the radio-opacity of these organs is so similar that the shadows usually merge into one. Dippel puts the matter thus: *"The placenta is localised in the region where the structures between the outer uterine wall and the foetal soft parts are definitely increased in thickness."*

Present Investigations

Using the described methods, a representative series of radiographs was obtained from normal patients in the last 8 weeks of pregnancy. In almost every case a localised thickening of the uterine wall could be seen clearly. A critical analysis was then made of some 30 films selected because of technical superiority. As a result of this study, many questions pressed for answer: among them were the following. Why should the placenta be so conveniently placed that its outline could be clearly seen in almost every lateral view? Why should the placenta be oftenest seen over the ventral surface of the foetus? (Snow and Powell state: "In practically all cases the ventral part of the foetus faces it.") Why should the placenta be difficult to visualize in cases of hydramnios? Why should the foetal limbs sometimes make such a deep indentation in the placenta? There seemed to be one common answer to all these puzzling questions. The thickening of the shadow of the uterine wall might represent not only the placenta, but also a localised excess of amniotic fluid.

Now, there is no reason to suppose that the foetus, surrounded by fluid, must necessarily remain poised in mid-cavity; it is far more probable that it usually rests with one surface applied to the uterine wall while the other is separated from it by a layer of amniotic fluid varying in depth in different cases.

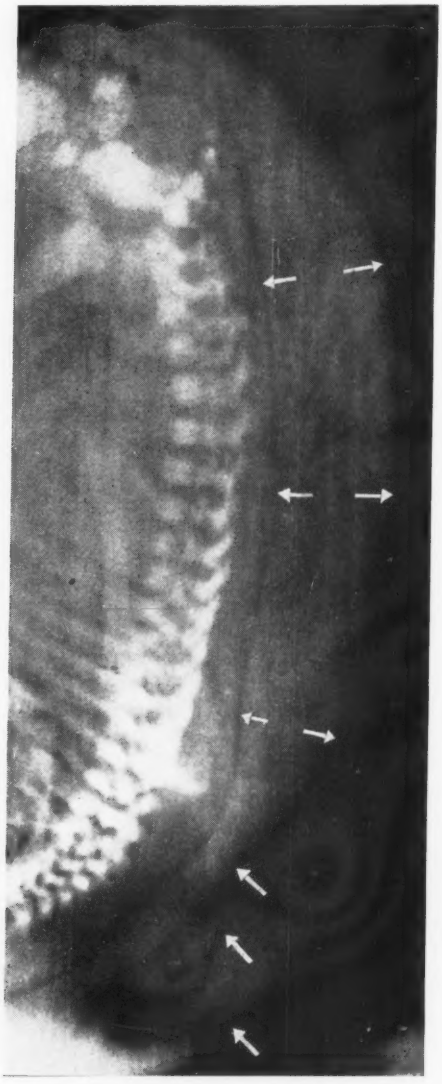

Fig. 1.—Lateral view of pregnant abdomen. The lower three arrows point to skin, abdominal-wall muscles, and outer surface of uterus respectively. The other indicate the local thickening of the uterine wall.

It was a basic assumption by Snow and Powell that in this method of placentography that the placenta and the liquor amnii cast shadows of different density. These writers state: ". . . the placenta consisting of tissues and blood causes a greater obstruction to the roentgen rays

than the amniotic fluid which is of low specific gravity. Hence the latter casts a blacker shadow.'' Yet, paradoxically, Snow elsewhere states that the placenta cannot be revealed in cases of hydramnios: ''the large quantity of fluid casts a shadow which cannot always be differentiated from that of the placenta.''[2] If, then, the placenta cannot be outlined

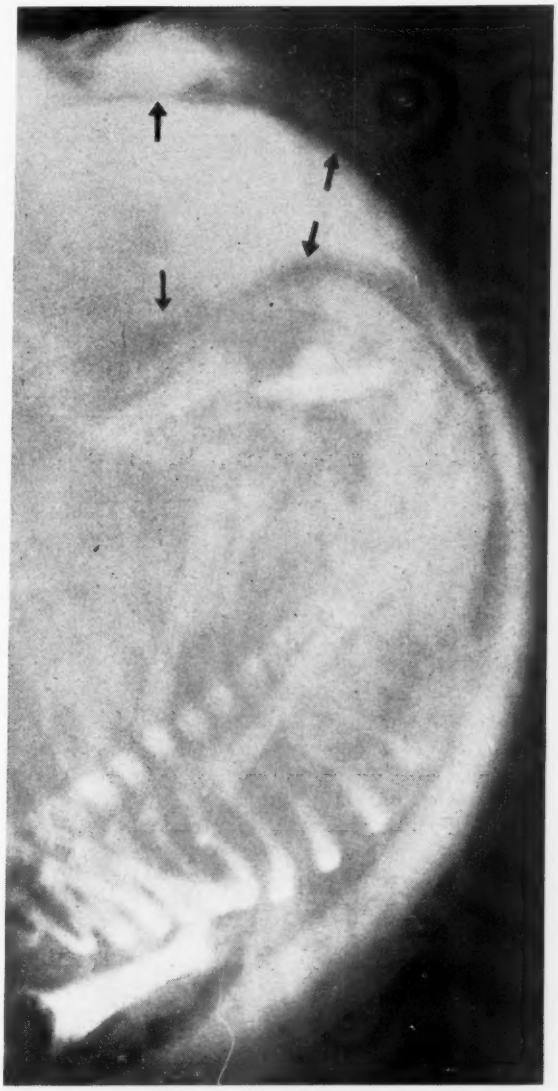

Fig. 2.—Lateral view of pregnant abdomen. Arrows indicate the local thickening of the uterine wall, situated in this case over the posterior part of the fundus.

against amniotic fluid when that is present in excess, by what new token can it be displayed against a background of the same fluid present in normal quantity? It seemed more probable that the uterine wall, the placenta and the amniotic fluid all cast shadows of similar density, and that the localised ''bulgings'' of the outline were often caused by

"pools" of normal amniotic fluid rather than by placental tissue. Various experiments were devised to put this supposition to the test, and these will now be described under six headings.

1. *Can Placenta Be Distinguished From Amniotic Fluid?*—Snow and Powell believed that in normal cases the amniotic fluid and placenta cast shadows of different density. It is far from clear that this assumption was ever justified, nor does it seem that their statement has since been critically examined. A simple experiment was devised to put the matter to test.

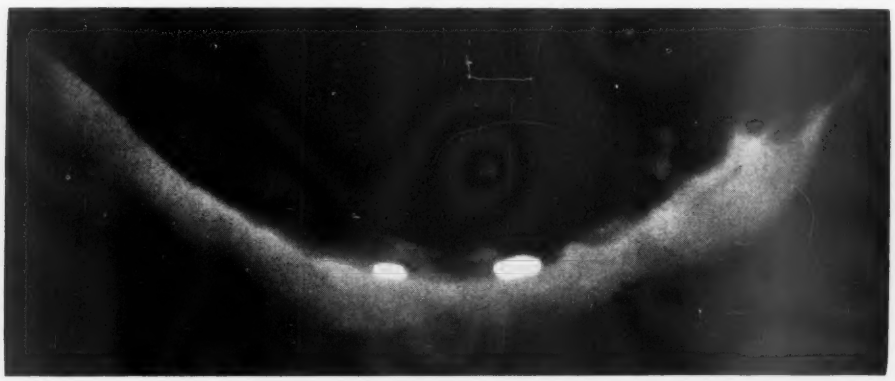

Fig. 3.—Lateral radiograph of a placenta suspended by its membranes from a wire loop 7" in diameter; the foetal surface is uppermost. The inner surface of the placenta can be easily seen; two small pieces of lead have been placed on the surface to make its identification certain.

A normal, fresh placenta, foetal surface uppermost, was attached by its membranes to a wire loop 7 inches in diameter. The organ thus assumed the shape it previously held in utero. A lateral radiogram was obtained, and, as was to be expected, the inner surface of the suspended placenta was clearly outlined (Fig. 3). A quantity of normal liquor amnii (obtained by catheter puncture) was now carefully poured into the saucer-shaped placenta, and a second radiograph obtained. The appearances were now completely changed: all trace of the inner placental surface had disappeared (Fig. 4). This experiment was repeated using three different placentas, with like results. Thus, even under the ideal circumstance of examining the isolated placenta, the radio-opacity of tissue and fluid proved to be too nearly alike to allow of any differentiation.

Regarding placenta and uterine wall, all workers agree that soft-tissue roentgenography of the pregnant abdomen will not enable one to be outlined against the other unless in the rare instance of a partly calcified placenta. The experiment now described enables the firm statement to be made that the uterine wall, the placenta and the amniotic fluid are all three so nearly alike in opacity that it is impossible to differentiate one from another by any usual method of radiological examination.

2. *The Nature of the Dark Band Surrounding the Foetus.*—In most radiographs of a full-time pregnant uterus the foetus is seen to be surrounded, for the most part, by a well-marked, dark band that varies in thickness up to about 75 mm. This dark, or relatively transparent, space appears to separate the foetus from the uterine wall, and at first sight

it is natural to regard it as the shadow of a layer of amniotic fluid; this assumption can lead to erroneous interpretation of radiographs of the pregnant abdomen.

The nature of the dark band has been the subject of considerable speculation; it has been attributed to the presence of a layer of vernix caeseosa, and even to a deceptive photographic effect. In 1939 Weintraub and Snow investigated this matter. They immersed a foetus in salt solution of a density equal to that of amniotic fluid and found that the foetal skin and subcutaneous tissue were considerably more transparent to the roentgen rays than the surrounding fluid or the underlying foetal muscle. The appearances seen in radiographs of the pregnant uterus were thus explained.

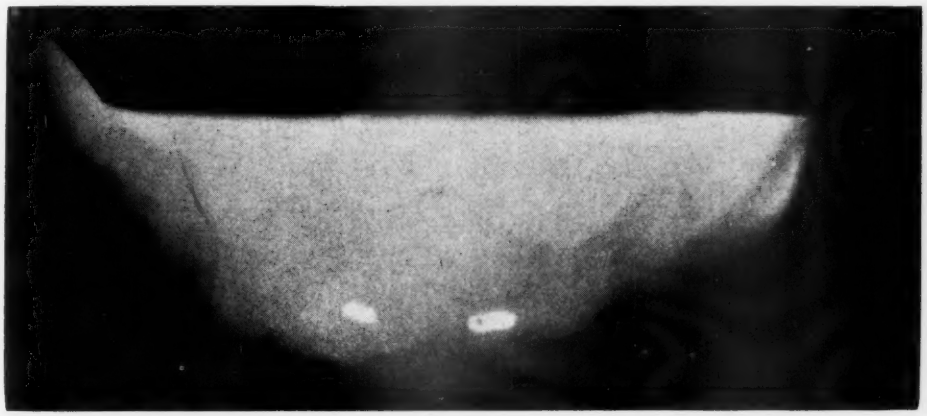

Fig. 4.—The same placenta after it had been partly filled with amniotic fluid. The inner surface has now completely disappeared although its position is indicated by the two pieces of lead.

As this interpretation was of fundamental importance concerning the matter in hand, it was decided to repeat Snow and Weintraub's experiment and to make it more realistic by using actual liquor amnii. Accordingly, the fluid obtained when the foetal membranes were punctured by catheter to induce labour, was used to fill a paraffin-waxed cardboard box. A full-time stillborn foetus was immersed in the fluid, and the radiograph shown on Fig. 5 was obtained. It will be seen that a dark band occupies the space between the muscle-tissues on the one hand, and the skin surface and the beginning of the amniotic fluid on the other. In other words, the subcutaneous tissue is considerably more transparent than either foetal muscle or amniotic fluid. A thin layer of foetal skin appears to equal, or even exceed, the opacity of the amniotic fluid. This experiment confirms, in the main, the previous finding by Weintraub and Snow that the dark band, so notable in many radiographs, is of foetal origin. *It does not represent a layer of amniotic fluid.*

In radiographs of the pregnant abdomen, the dark layer can be identified with certainty. It is found to be thickest in those regions where the foetal fat is best developed—over limbs and buttocks—but it is scarcely visible where fat is absent, as, for example, over the skull. It is much in evidence when the foetus is large, but is only seen with difficulty when the foetus is premature. The *outer* margin of the dark band marks the foetal skin, and may mark the beginning of the uterine wall or placenta;

but, as has been shown, it may equally well mark the beginning of a layer of amniotic fluid. It is often impossible to decide between these three possibilities.

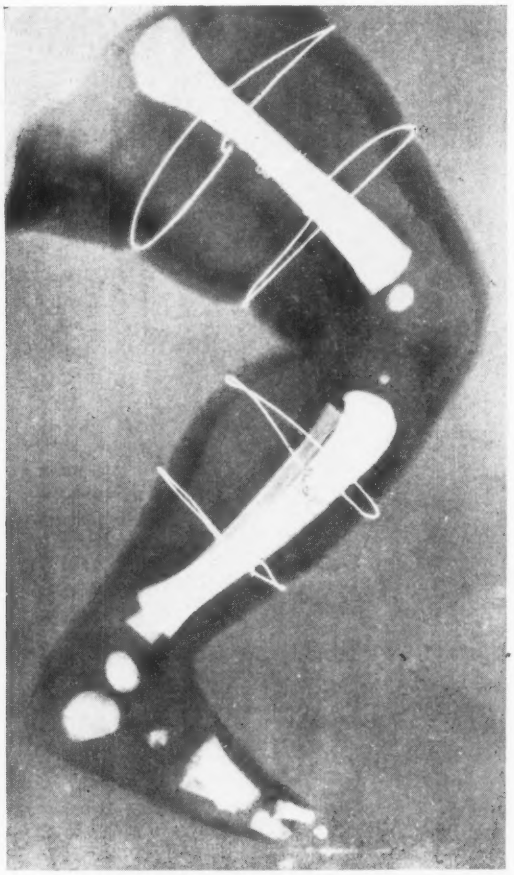

Fig. 5.—Limb of a foetus radiographed while completely immersed in liquor amnii. Lead wires twisted around leg indicate position of skin surface. The dark band surrounding the limb is caused by the relative transparency of the subcutaneous tissues. A thin layer of skin approximates—or very slightly exceeds—the opacity of the amniotic fluid.

3. *The Thickness of the Placenta.*—The radiographs published by Snow, Dippel and their co-workers, show that the space described as placental shadow is, in some cases, surprisingly thick. No measure is included in the pictures, but by indirect methods a fairly accurate estimate of the thickness can be made. Thus, in some of the lateral views, the maternal lumbar vertebrae are clearly seen. If one assumes that the anterior surface of the 5th lumbar vertebra measures, from above downward, approximately 3.2 cm., this span can be used to judge the distance between the outer wall of the uterus and the inner surface of the shadow stated to be placenta.

Snow and Powell's reproductions are made from direct tracings of full-sized radiographs. Six of these were carefully examined. The thickness of placenta plus uterine wall was estimated to be 3.4, 4.0, 4.8, 4.8, 6.5, and 7.2 cm. respectively. Two of Snow and Rosensohn's repro-

ductions of radiographs were similarly examined. The measurement was 6.2, and 5.6 cm. respectively. In one of Dippel and Brown's radiographs the measurement was 8.3 cm. If from these figures is subtracted the normal thickness of the uterine wall (stated by Snow to be 1.5 cm., and by Dippel and Brown to be 1.24 cm. in the magnified radiographic shadow), it will be seen that the thickness of the placenta was never less than 2.5 cm. and in one case was more than 5.7 cm.

To determine the usual placental thickness, twenty-five unselected placentas were collected and laid on a stone slab; the organ was transfixed with a needle and the thickness marked on the shaft. The measurements were as follows: 2 cm. or under, 4 cases; 2.1 to 2.5 cm., 9 cases; 2.6 to 3 cm. 11 cases; 3.1 cm. one case.

These measurements refer to the expelled, semi-retracted placenta. The true thickness of the organ when fresh and attached to the uterine wall may be less. In three cases I have been able to get measurements of the placental thickness from uteri that have been fixed with contents in situ. In one case (a seven-months' gestation) it measured 2.9 cm. There was, however, a considerable formation of gas in the tissues, and this measurement may therefore be misleadingly great. The two other cases were of full-time gestations: in one the placenta was less than 1.5 cm., in the other it was less than 2 cm. In Barbour's *Anatomy of Labour* the majority of drawings (based on post-mortem specimens) show a placenta below 2 cm. in thickness; in two cases the thickness appears to be between 2.5 and 3 cm., and in one case it is (very vaguely) about 3.4 cm.

Assuming that the placenta rarely exceeds 3 cm. in thickness, it will be realised that nearly all the illustrations published in support of soft-tissue placentography reveal a "placenta" of great size, the thickness in one case amounting to nearly twice the maximum probable measurement. There is thus strong presumptive evidence that the shadows under consideration were produced partly, or wholly, by amniotic fluid.

As already stated, it is significant to find that Snow realizes this possibility of error. He writes:[3]

"If hydramnios is present its shadow runs together with that of the placenta. It then appears as if the placenta were completely surrounding the foetus. Since this is extremely unlikely, the diagnosis of hydramnios is made."

Thus, in the original description of soft-tissue placentography, a fallacy is admitted, although its full significance does not seem to have been appreciated. It is not unfair to paraphrase Snow's words thus: *If the shadow in question resembles a placenta in shape, the organ has been identified: If, however, it does not agree with one's preconceived idea of placental shape and thickness, then this otherwise identical shadow must represent amniotic fluid.* It is difficult to accept such reasoning; if a "large" shadow is caused by fluid, why should a smaller shadow not be caused by the same fluid in smaller amount? In a previous section it has been shown that amniotic fluid and placenta do, in point of fact, cast shadows indistinguishable in density. It is thus evident that the diagnosis rests essentially on a similarity to the supposed shape of a placenta in utero, and on this basis there can seldom be any warrant of certainty.

In fairness it must be added that in many instances the shadows in question *may* represent placenta. With experience, one's interpretation of radiographs will also become more reliable. Nevertheless, the defini-

tion of placental shadows as given in the earlier descriptions of this method of radiology is seriously misleading, and re-definition is urgently required.

4. *The Indentations on the "Placental" Surface.*—Snow and Rosensohn mention a frequent indenting of the placenta by the foetal limbs; these irregularities they term "digitations," and they believe that they are caused by uneven pressure on the soft placental tissue. In the present investigation, many examples of such indentations were encountered; often they were surprisingly deep (Fig. 6). In Snow's own

Fig. 6.—Indenting of "placental" shadow by the hand and the shoulder of the foetus.

pictures the placenta is reduced to a half or even a quarter of its thickness by these pressure marks—a fact surprising to anyone familiar with the normal texture of placental tissue. The irregularities might be caused by the rays striking the abdomen at such an angle as to show overlapping of shadows: this possibility is considered by Snow but dismissed as an incomplete explanation. If, however, the proposition is accepted that the shadow in question is caused by amniotic fluid, then the irregularities of that shadow are readily understood.

It is not denied that the placental surface may sometimes be slightly indented by projecting foetal limbs—this is especially likely when there is less than the usual quantity of amniotic fluid. But the sharp and

deep indentations so often seen in the substance surrounding the foetus are, almost certainly, of a different nature. They are the natural consequence of radiographing foetal parts against a fluid background.

Fig. 7.—Tracing of radiograph showing a thick anterior "placental" shadow. The dark band caused by the relative transparency of the foetal subcutaneous tissue is also indicated.

5. *Effect of External Pressure.*—The thickening of the uterine-wall shadow is frequently confined to the anterior surface. If, as has been postulated, this thickening is, in most instances, due to a local excess of amniotic fluid, it should usually be possible to alter the appearance by applying external pressure. Experiments have confirmed this expectation.

Patients were selected who showed anteriorly situated thickenings of the uterine shadow, corresponding to the original description of placental site. Examination was made with the women standing in the erect position. After the first exposure a sheet of firm cardboard was used to indent the abdominal wall where the uterine shadow was broadest. In the example illustrated (Figs. 7 and 8) it will be seen that the pressure has had the effect of reducing the thickness of the shadow to nearly a third of its previous dimension. Bearing in mind that the uterine wall itself is approximately 1.25 cm. in thickness, it will be

realised that the "placenta" has been reduced to a still smaller fraction of its previous thickness. Such a change as this is incomprehensible except on the basis that it represents a displacement of amniotic fluid.

6. *Displacement of Amniotic Fluid by Air.*—Continuing these experiments, another method of displacing the amniotic fluid was put to test. A small quantity of air was introduced into the amniotic sac, and radiographs were then obtained with the patient positioned to show the air-bubble in relation to the supposed placental tissue.

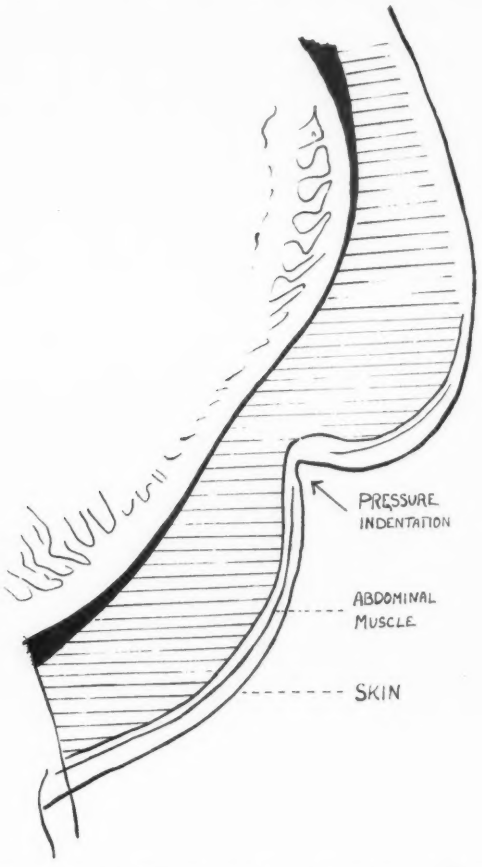

Fig. 8.—From same patient as Fig. 7, showing effect of external pressure on the supposed placental shadow.

The patients selected were due to have labour induced by perforation of the foetal membranes. With the usual technique, a Drew-Smythe catheter was introduced, and the amniotic sac punctured above the presenting part. After several ounces of fluid had freely escaped, air was carefully injected to the amount of about 100 c.c. Examination was then made with the patient first in the erect, then in the horizontal position.

In the example shown (Figs. 9 and 10) the patient appeared to have an anteriorly situated placenta according to the original definition; after the air injection this localised thickening completely disappeared and the

uterine wall was revealed in its true thickness. All suggestion of placenta had vanished! A similar result was obtained in a case in which the foetus presented by the vertex, and in which the "placental" thickening was situated between the anterior wall of the uterus and the thorax of the foetus.

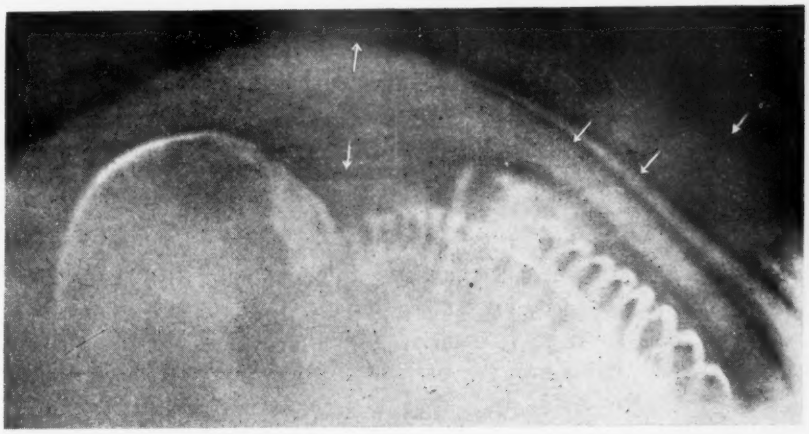

Fig. 9.—Anteriorly situated "placental" shadow from a case in which the foetus presented by the breech. The arrows on the right indicate skin, abdominal-wall muscles and outer uterine surface respectively. Arrows on left indicate extent of the "placental" bulge.

Fig. 10.—Radiograph of same case as Fig. 9, after air had been introduced into the amniotic sac. The bulge has now quite disappeared and the uterus is seen to be normal in thickness at the site of the supposed placenta.

This last test finally disposed of any doubt regarding the nature of the localised thickening of the uterine shadow in the cases investigated. The shadow has proved to be partly, and much oftener, wholly, the result of an uneven positioning of the foetus in the uterine cavity with consequent uneven distribution of surrounding fluid. It is impossible in any ordinary radiograph to distinguish between placental tissue and a local excess of amniotic fluid.

Conclusions

1. Serious errors of interpretation are likely to occur in the use of the soft-tissue method of placentography as originally described.

2. Experiments show that the dark band surrounding the foetus in utero is the result of the relative transparency of the subcutaneous tissue of the foetus. It does not represent amniotic fluid: the conclusions of Weintraub and Snow are in the main confirmed.

3. Experiments are described which prove that the uterine wall, the placenta, and the amniotic fluid are all similar in radio-opacity. A local collection of amniotic fluid (caused by an uneven position of the foetus in utero) gives a shadow indistinguishable on ordinary examination from placental tissue. The shape of the shadow may give a clue to its identity but certainty in diagnosis is seldom possible on this basis alone.

4. Critical examination of previous work raises doubt regarding the accuracy of the interpretation of the experimental findings. In some of the radiographs the thickness of the "placenta" considerably exceeds the thickness of the normal organ.

5. The deep indentations frequently seen on the "placental" surface can be readily explained on the basis of the fluid nature of the shadow-producing substance.

6. In test cases, the localised thickening of the uterine-wall shadow (the placental site according to the original definitions) disappeared when external pressure was applied.

7. In test cases, air introduced into the amniotic sac revealed a uterine wall of normal thickness at the site of the supposed placenta.

8. Positive findings from this method of placentography should be accepted with reserve: negative findings may have a limited field of usefulness.

Postscript.—Since this paper has been in preparation two further publications on soft-tissue placentography have appeared. Lloyd and Samuel[9] use a tomographic technique: in a short series of cases their results seem to be similar to those of previous workers. Buxton, Hunt and Potter[10] claim successful indentification of the placenta in 86.1 per cent of 108 cases: when in doubt they resort to the older method of cystography. Nothing in these more recent publications calls for modification of the opinions already expressed.

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Comment

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Our experience with this method does not coincide with that reported by Moir in that the method gave a favorable impression from the outset and has continued to do so. Moreover, the number of roentgenograms considered unsatisfactory for purposes of interpretation has decreased with experience. Likewise, confusing shadows have been clarified. Notable among these has been what we have called the "nuchal" shadow and which is shown in Moir's Figs. 6 and 9. In the early days of our work, Brown and I recognized that these were not shadows of the placenta. They could not have been because the placental shadow was definitely localized elsewhere on the wall of the uterine cavity. We thought at first that this (Fig. 6) represented a thickened portion of the uterine wall marking the division between the upper and lower uterine segments. However, when we began seeing similar shadows well up on the uterine wall in association with breech positions (Fig. 9) we realized the error of our original interpretation and thereafter ignored such shadows except as collections of amniotic fluid between the uterine wall and skin of the fetal neck. Very little experience should be necessary in recognizing that these shadows could not possibly represent placental areas for they are too atypical in appearance and do not coincide with our knowledge of the size and shape of the placenta viewed in profile. One would avoid the possible errors in Figs. 6 and 9 by visualizing the whole of the uterine wall and not focusing attention on localized atypical areas of apparent thickening of the wall. We do not consider a roentgenogram adequate for purposes of visualization of the placenta unless the whole of the uterine wall above the bony pelvis can be made out.

Mention must also be made of Moir's error in explaining why lateral views are used and anteroposteriors are valueless. This is not because gestational shadows may be obscured by the relatively denser maternal shadows in the anteroposterior view but because the placenta is almost always implanted primarily over the relatively flat anterior or posterior uterine wall and rarely extends over the dividing lines between these. This has been well demonstrated by Torpin's method of amniotic sac distension, and we have made reference to this in our previous articles. Such being the case one would have to look at a lateral view in order to see the placenta in profile. We have never visualized the placenta except in a lateral view and no longer resort to anteroposterior views in attempting to visualize the placenta by soft-tissue roentgenography.

As for distribution of placental sites on the various areas of the uterine wall, we do not agree with Moir's experience. We have not observed any predilection for the anterior wall of the corpus uteri. In our last report in which the placenta was clearly visualized in 236 patients, there were almost exactly as many placentas implanted on the posterior as on the anterior wall of the corpus. In the smaller number implanted over the lower uterine segment, 26 cases, we observed a greater incidence of anterior implantations, a ratio to posterior implantations amounting to 8:1.

Moir's experiments constitute the major contribution of this paper but cannot all be accepted as final proof. While we have never doubted the indistinguishable nature of the placental and amniotic fluid shadows in the majority of roentgenograms, one cannot accept, as conclusive proof, his x-ray demonstrations of the delivered placenta. The undelivered and functioning placenta is not roentgeno-

graphically the same organ as the delivered placenta, which contains less blood. That the dark line separating the term fetus from its surrounding structures is due to subcutaneous fetal fat has long been accepted. It conforms too well to the fetal outline to be associated with anything but the fetal skin. Weintraub and Snow settled this argument in 1939. Furthermore, in unpublished works on vernix caseosa, Brown demonstrated that this waxy material cast a radiographic shadow different from the one surrounding the fetus.

The demonstration of the possible dual nature of a "placental" shadow is very clearly shown in the sketches of Figs. 7 and 8. It must be emphasized, however, that the applied pressure did not disprove the presence of placenta beneath the anterior uterine wall. Actually, it proved its presence there in conjunction with some amniotic fluid. Had this shadow been made up entirely of amniotic fluid, he should have been able to displace it completely by external pressure.

From what has already been said of localized atypical apparent thickenings of the uterine wall such as the "nuchal" shadow shown in Fig. 9, our group would never have made the mistaken diagnosis even without injection of air, but the experiment is a beautiful demonstration with conclusive proof. Moir appears to be unduly upset about our American way of calling a placental shadow a placenta simply because it fits our knowledge of the appearance of a placenta. We can see no reason why only a radiographic shadow which fits our preconceived idea of size and shape of the placenta should not be called a true placental shadow, whereas, if it does not meet these requirements it should not be called something else, such as excessive amniotic fluid. Quite aside from the logic of such reasoning, it must be admitted that no errors have been produced in soft-tissue localization of the placenta when strict criteria of that nature have been adhered to. Thus, at the time of our last analysis, the placental site had been checked in 22 per cent of the cases with acceptable films.

The fact that the radiodensities of uterine wall, placenta, and amniotic fluid are nearly the same in no way lessens the value of soft-tissue localization of the placenta. We have shown that in 90 per cent of lateral roentgenograms, it is possible to demonstrate uterine wall of normal thickness either anteriorly or posteriorly while the opposite wall appeared to be thickened. It was also pointed out that this area of apparent thickening fitted more or less our previously formulated ideas of size and shape of the placenta in profile. Whether the latter shadow is made up of placenta and amniotic fluid or placenta alone has not disturbed us for the fact has remained that the shadow either comprises or contains the placenta. The purpose of the special study is only to locate the placental site. In our experience, the size and shape of the shadow has supplied positive evidence of the location of the placenta, and, with normal appearance of the opposite uterine wall, has been the sole basis for localization. The experience of many clinics with hundreds of cases would seem to substantiate our views.

The reproduced roentgenograms of this paper are of high quality and strongly indicate that Moir's difficulties have been with interpretation and not with techniques. His criticisms are indictments not of the method but of unacceptable criteria used in interpretation.

SURGICAL PROBLEMS ARISING DURING PREGNANCY*

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DURING the past eleven years approximately 40,000 pregnant women have been admitted to the New York Hospital. In this group of patients, 120, or 0.3 per cent, presented surgical or gynecological problems arising during the course of their gestation. These are tabulated together with relevant mortality data in Table I. The authors are well

TABLE I. OPERATIONS PERFORMED DURING PREGNANCY

NEW YORK HOSPITAL. 1932 TO 1943

OPERATION	NO. OF CASES	MATERNAL MORTALITY	ABORTIONS		FOLLOW-UP		
			DUE TO OPERATION	NOT DUE TO OPERATION	LOST	FOL-LOW'D	TERM DELIVERY
Minor Surgical	16	0	0		0	16	16
Major Surgical (nonabdominal)	8	0	0		0	8	8
Major Abdominal (surgical)							
Appendectomy (non-perforated)	36	0	0		12	24	24
Appendectomy (perforated)	4	2	2		0	2	2
Cholecystectomy (2 ac.; 2 chr.)	4	0	0		1	3	3
Resection of ileum (gangrene)	1	1	1				
I. & D. intra-abdominal abscess	1	0	1			1	
Miscellaneous	6	0	0		0	6	6
Total		3	4		13	60	59
%		3.9	5.3		17.1	78.9	77.6
Major Abdominal (gynecological)							
Oophorocystectomy	23	0	4	1	3	20	15
Myomectomy	11	0	5	1	0	11	5
Miscellaneous	10	0	1	4	0	10	5
Total	44	0	10	6	3	41	25
%		0	22.7	13.6	6.8	90.8	56.8
Total	120	3	14	6	16	101	84
Surgical and gynecological cases							
Per cent		2.5	11.7	5	13.3	84.1	70

aware of the fact that since this subject has received such extensive consideration in the past, there might be little reason for presenting another relatively small series of cases. However, because the fetal

*Presented at a meeting of the New York Obstetrical Society, October 12, 1943.

and maternal mortality continues to be relatively high, because the problem has received scant statistical attention in the past few years, and because these patients have all been treated by closely coordinated surgical, obstetrical and gynecological services under a full residency regime, it has been deemed important to record the experiences of this institution.

In order to facilitate the study these cases have been divided into appropriate groups according to the nature of the operation performed.

I. Minor Surgical Operations.—This comprises a total of 16 patients upon whom such relatively minor procedures as incision and drainage of an abscess, excision of a benign breast tumor, and ligation and excision of varicose veins, were performed. Local or light gas-oxygen anesthesia was employed in these operations and, as should be expected, there was no associated fetal or maternal mortality. Since these patients failed to present any significant surgical or obstetrical problems they may be dismissed without further discussion.

II. Major Nonabdominal Operations.—This next group deserves brief but serious attention. It is composed of eight patients upon whom major, but not abdominal, procedures were performed. These are outlined in Table II, and consist of one radical mastectomy for cancer; two

TABLE II. NONABDOMINAL MAJOR OPERATIONS

OPERATION	NUMBER CASES	MONTH	MORTALITY
Radical mastectomy for cancer of the breast	1	3rd	0
Nontoxic adenomata of thyroid	2	3rd, 5th	0
Melanosarcoma of back, excision	1	3rd	0
Craniotomies	2	6th, 8th	0
Radical mastoidectomy	2	8th, 6th	0
Total	8		0%

thyroidectomies for nontoxic goiter; an extensive excision of a melanosarcoma of the back; two craniotomies, one for chronic arachnoiditis associated with increased intracranial pressure, and one for cerebellar abscess; and two radical mastoidectomies in acutely ill patients. These cases were distributed about evenly from the third through the eighth month of pregnancy, and it is considered significant that, in spite of the seriousness of these operations, all of these women delivered normally at term.

III. Major Abdominal Operations.—This comprises the largest single group of patients presenting surgical complications during their pregnancy, and is composed of two types of cases—those operated upon for reasons that may be termed surgical in their nature, and those in which the operative indications were in general gynecological. Since these two groups present a number of fundamental differences they have been considered individually by the authors, the first by C. G. C., the second by R. G. D. All of these cases have been subjected to analysis from the conventional points of view including history, physical examination, laboratory studies, vital signs, anesthesia employed, cultures taken at operation, etc. Since most of these data proved to be of relatively minor

significance, they have been omitted here as being noncontributory to the problem as a whole. Only those features deemed of interest will be considered.

General Surgical Cases

There were 52 patients in whom the major abdominal operation was performed because of indications which have been termed surgical in nature. The first point of view from which these cases were studied concerns the correctness of the preoperative diagnosis. Excluding 11 cases, such as biliary tract disease, strangulated herniae, and a few others in which the preoperative diagnosis was self-evident, there remains a group of 41 patients. In all of these a clinical diagnosis of acute appendicitis was made prior to operation. This proved to be correct in 25 instances, but incorrect in 16. In other words, a correct preoperative diagnosis was made in all of the patients proving at operation to have had acute appendicitis in one or another of its forms; in sixteen, however, other pathologic entities were found within the peritoneal cavity. A brief summary of these patients will be found in Table III. When one considers the handicaps to accurate surgical diag-

TABLE III. 16 CASES INCORRECTLY DIAGNOSED BEFORE OPERATION
PREOPERATIVE DIAGNOSIS IN ALL—ACUTE APPENDICITIS

DIAGNOSIS	OPERATION	NUMBER CASES	MONTH	MORTALITY	
				MATERNAL	FETAL
Twisted ovarian cyst	Resection of cyst	2	4th, 6th	0	0
Chronic appendicitis	Appendectomy	6	2nd thru 8th	0	0
Acute salpingitis, with peritonitis	Appendectomy	1	5th	0	0
Pedunculated myoma, gangrenous	Resection myoma	1	7th	0	0
Acute pyelitis	Appendectomy	2	5th, 6th	0	0
Torsion of fallopian tube	Resection of tube	1	8th	0	0
Gangrenous hydatid of morgagni	Resection hydatid	1	9th (Cesar. section eclampsia)	0	0
Acute gastroenteritis	Appendectomy	2	both 2nd	0	0
		16		0%	0%

nosis which the gravid uterus superimposes upon an already difficult problem, it is perhaps a wonder that the number of inaccuracies was not greater. It is of course gratifying to note that there was no maternal or fetal mortality in any of these patients. The patient in whom a gangrenous hydatid of Morgagni was resected perhaps deserves a further word of comment. She developed her acute abdominal symptoms at term and shortly following operation presented signs and symptoms of eclampsia. It was for this reason that the cesarean section was performed, not because of the surgical procedure or disease.

Appendicitis During Pregnancy

The largest and most interesting single group of patients in this series is that involving the appendix. The subject of appendicitis in pregnancy has been one open in the past to no small amount of discussion. Much of this can apparently be traced back to the time when the correct treatment of appendicitis itself presented far greater problems than it does today. Appendicitis uncomplicated by pregnancy was a serious and often a lethal disease; and when the pregnant state was added to it, the patient's plight apparently became precarious indeed. Hence, the early literature upon this subject is replete with dire warnings and implications based more upon fear of the combined problems than upon actual knowledge of the various factors involved. The observation that many women died when appendicitis complicated pregnancy or vice versa led to many ill-founded and unfortunate impressions. The high mortality produced a number of beliefs, namely that pregnant women are less well able to withstand infection, that the displaced appendix is more prone to rupture, that the peritoneal cavity is unable during pregnancy to wall itself off adequately, and that the increased vascularity is in itself serious in the presence of an acute septic process. Upon these conceptions was formulated a therapeutic policy which in all likelihood contributed to increase rather than to decrease the high mortality. The early plans of attack involved the principle of removing the appendix and emptying the uterus as nearly simultaneously as possible. This led to such combined operations as cesarean section, followed by exploration of the appendix and its removal, or appendectomy followed promptly by some form of accouchement forcé. These operative procedures, particularly if combined with a sufficiently generous delay during which time the appendix frequently ruptured, proved more than many an unfortunate patient could reasonably be expected to tolerate. It is little wonder that the mortality was high. As time has gone on, however, and knowledge of appendicitis has increased, most of these erroneous impressions have been discarded, and the present approach to the problem of appendicitis in pregnancy adopted. This group of patients has been treated with the principle clearly in mind that the only correct treatment of appendicitis during gestation rests securely upon early operation, and that the pregnancy be allowed to progress undisturbed save for purely obstetric reasons.

In reviewing a number of reports upon this subject two findings have been repeatedly noted;[1-4] one, that by far the greatest number of cases of appendicitis occur during the early months of pregnancy, and two, that when appendicitis does occur late it usually does so in its more severe forms. In this respect this series is no exception; 18 appeared in the first trimester, 12 in the second, and 6 in the last. (Table IV.) Furthermore, three of the four cases in which perforation occurred appear in the last two months and the only two maternal and fetal

TABLE IV. APPENDECTOMY DURING PREGNANCY

MONTH	NORMAL	CHRONIC	ACUTE WITHOUT PERFORAT.		ACUTE WITH PERFORATION		TOTAL PER MONTH
			DIFF. SUPPURAT.	GANGRENOUS	ABSCESS	GEN'L. PERITON.	
1st		2	5		1		8
2nd	2	1	2				5
3rd		4	3				7
4th			5	(2)			5
5th	1 pyelitis	1	2				4
6th	1 pyelitis	1	3				5
7th		1					1
8th			1			2 2 deaths	3
Term		1				1	2
Total	4	11	21		1	3	40

1st trimester 18 cases 2nd trimester 12 cases
3rd trimester 6 cases

deaths are found in the eighth month. A number of explanations have been advanced in the past to account for this phenomenon, most of them involving such vagaries as the early displacement of the appendix precipitating appendicitis, and the lessened ability of the peritoneal cavity to withstand infection in the presence of the gravid uterus, etc. These, however, hardly seem adequate. It is suggested, therefore, that actually appendicitis is quite as common in the last two months as it is earlier but that the diagnosis is far less frequently made. This postulation, which was true in the series of Norton and Connell,[5] seems to be substantiated logically by several facts: First, that the presence of the gravid uterus renders the diagnosis more difficult to make at or near term. Second, the multitude of abdominal signs and symptoms that tend to appear late in pregnancy are often difficult to evaluate correctly. Third, it is well recognized that many attacks of acute appendicitis subside spontaneously. Thus, it seems reasonable to conjecture that a number of attacks of this disease in its acute form pass unrecognized in the seventh, eighth and ninth months. Particularly does this seem to be true when the natural hesitancy of obstetricians and surgeons to complicate a term pregnancy by an operation is appreciated. As far as the greater seriousness of appendicitis late in pregnancy is concerned, the explanation seems apparent, namely that only those attacks progressing to rupture and subsequent peritonitis are recognized.

If this concept be correct, the only course by which the mortality from this disease is to be lowered significantly lies in making a diagnosis early enough to operate upon these patients before perforation has occurred. Particularly is this true when one considers that the mortality in unruptured appendicitis is in this series zero, and among the general population less than 0.2 per cent.[7] The tragic sequelae of perforation can be

prevented only by according abdominal complaints more careful attention during the last trimester, and operating earlier and in greater frequency upon those who might be suspected of having the disease in its simple acute stage. As is adequately demonstrated not only by this but by other series of cases of this type, mothers do not die nor are babies lost as a result of an uncomplicated celiotomy. If the policy of earlier and more frequent operation is adopted for what may seem at the time relatively benign symptoms and signs, it may be anticipated that a certain number of pregnant women will be operated upon needlessly. In view of the all but negligible risk involved, it is apparent that this is a small price to pay compared to the tragedy that follows the rupture of but one appendix. This approach to the general problem of appendicitis is one for which surgeons have not infrequently been criticized. That it has withstood the test of time, however, is reflected in a steadily decreasing mortality rate in appendicitis and that it has a definite place in the armamentarium of general surgery is becoming increasingly obvious. It should, therefore, find a similar application in this disease as it arises during the course of pregnancy.

The next point of interest is found in a consideration of both the immediate and late results in these patients in whom appendectomy was performed during the course of their gestation. The hospital mortality and follow-up results are briefly outlined in Table V. Out of the entire

TABLE V. FOLLOW-UP STATISTICS—40 CASES OF APPENDECTOMY

DIAGNOSIS	NUMBER CASES	HOSPITAL MORTALITY		FOLLOW-UP		MORTALITY
		MATERNAL	FETAL	LOST	TERM. DEL.	
I. Normal	4	0	0	2	2	0
II. Chronic	11	0	0	3	8	0
III. Acute without perforation	21	0	0	7	14	0
IV. Acute with Perforation — abscess	1	0	0	0	1	0
IV. Acute with Perforation — peritonitis	3	2	2	0	1	66%
	40	2	2	12	26	

Total Mortality—Maternal 5.0%
Fetal 5.0%

group of 40 cases, two mothers and two infants were lost, giving a gross mortality of five per cent. In those unperforated there was no maternal mortality nor were there any abortions or premature deliveries. As soon, however, as perforation complicated the picture, two out of the four mothers and their two infants were lost. The two remaining cases with perforation survived, one with a localized abscess occurring in the first month of pregnancy, and one with generalized peritonitis at term. Two out of the three patients with generalized peritonitis at or near term succumbed to their disease giving the high mortality rate of 66 per cent.

Although admittedly this series of cases is small, it lends added credence to the impression that generalized peritonitis at or near term is

a serious problem, any predictions as to the outcome of which must be guarded. Nor is our clinic alone in this experience. Smith and Bartlett[7] in 1940 reported a series of similar cases from the Boston Lying-in Hospital. These authors noted that three of their four cases of perforated appendicitis not only appeared in the last two months, but also died; while the fourth case, a woman four months pregnant, recovered only after a long and stormy course.

Major Abdominal, Exclusive of Appendicitis

In progressing now to consideration of the remaining patients subjected to a major abdominal operation, the outstanding feature is that by far the greatest number of these individuals presented acute surgical problems demanding more or less immediate operation. These are outlined in Table VI where the relevant statistical data may be found. The

TABLE VI. MAJOR SURGICAL ABDOMINAL CASES, EXCLUSIVE OF APPENDICITIS

DIAGNOSIS	OPERATION	NUMBER OF CASES	MONTH OF PREGNANCY	HOSPITAL MORTALITY		FOLLOW-UP	
				MATERNAL	FETAL	LOST	TERM. DEL.
Acute cholecystitis Cholelithiasis	Cholecystectomy (2)	2	3rd and 4th	0	0	1	1
Chronic cholecystitis Cholelithiasis	Cholecystectomy (2)	2	2nd and 3rd	0	0	0	2
Strangulated hernia	Repairs (3)	3	2nd and 4th and 8th	0	0	0	3
Chronic pyelonephritis	Nephrectomy	1	3rd	0	0	0	1
Ureteral Calculus	Ureterolithotomy	1	5th	0	0	0	1
Acute intestinal obstruction, Perforated Ileum, Intraabdominal abscess	Resection of ileum with drainage	1	6th	1 (19 days p.o.)	1 (1 day p.o.)	Mother and fetus died	
Acute intraabdomin. abscess in Left lower quadrant	Incision and drainage	1	4th	0	1 (3 days p.o.)	Mother discharged well, with fecal fistula, abortion	
Totals		11		1	2	1	8

four patients with biliary tract disease, the three with strangulated herniae, and the two urological problems serve to re-emphasize the point already made that pregnant women can be operated upon with relative impunity. In this group the most interesting cases are the last two. The first of these was referred to the surgical service after having been treated unsuccessfully in two other hospitals for intestinal obstruction due to postoperative adhesions. When first seen she was desperately ill and went on to develop a gangrenous loop of ileum with perforation and multiple intra-abdominal abscesses. One day following resection of the

involved ileum she aborted, and nineteen days later expired in spite of all forms of supportive therapy. This patient presented a complicated surgical problem in which the pregnancy apparently played a relatively minor role. The last patient was explored because of a mass in her left lower quadrant. Following drainage of a large intra-abdominal abscess, the etiology of which was never adequately explained, she was acutely ill. She aborted on the third postoperative day, but ultimately recovered though she was discharged with a fecal fistula.

This group of patients reflect a firmly ingrained tendency not to subject women during gestation to operation unless it becomes imperative. It may be supposed justly that many more pregnant women than are operated upon present themselves during their ante-natal course with chronic surgical disease. Advice is undoubtedly given them to postpone, if possible, any operative intervention until after delivery. Of these it is reasonable to suppose that the majority deliver without developing an acute problem which demands operation. Still there are a significant number who develop an acute exacerbation of their disease, and of these a certain percentage, true it is small, will succumb. Particularly is this true when the disease carries with it the possibility of an associated peritonitis. It is not justified, of course, to interpret this attitude as indicating that all pregnant women presenting surgical problems in a quiescent state should be operated upon. It should mean, however, that operation need not be withheld in those patients presenting a sufficient number of signs and symptoms to make the development of an acute episode a real possibility.

Before leaving the patients who were subjected to abdominal operation primarily upon surgical indications, one significant phase deserves comment, namely, the outlook in the future for patients who, despite having had everything possible done to prevent it, ultimately present themselves with a generalized peritonitis, associated with pregnancy. For several reasons it seems justified to assume that their chances of recovery will be far greater in the future than they have been in the past. First, the greater safety in approaching acute right lower quadrant problems through a McBurney incision has been firmly established. Second, the parenteral and perhaps local use of the sulfonamides will undoubtedly contribute to decreasing the severity of the septic process. Third, the use of continuous enteric suction can be relied upon to improve the treatment of the adynamic type of intestinal obstruction that so frequently follows generalized infection of the peritoneal cavity. And, fourth, an increased understanding of water, electrolyte and protein balance will unquestionably aid these unfortunate patients in overcoming their acute illness. These, combined with a rigid laissez-faire policy from the obstetric point of view, all point toward a lowered mortality in the future.

Gynecological Cases.—The next group of cases in which a surgical problem complicated the pregnancy is that in which a major abdominal operation was performed because of the presence of an ovarian tumor,

a myoma, or some other suspected gynecologic lesion. In contrast to the general surgical cases in which the majority of patients presented acute problems, the operations in this group may be considered to have been more of an elective nature.

Corresponding to the minor surgical operations there was a group of patients who were operated upon during pregnancy for minor gynecologic lesions, such as congenital abnormalities, cysts of the lower genital tract, condylomata, etc. Since these procedures were unassociated with any untoward effect upon the course of the pregnancy, they were not considered sufficiently important to merit consideration here in further detail.

The largest single group is composed of 23 patients who were operated upon for removal of ovarian tumors (Table VII). In these there

TABLE VII. OOPHOROCYSTECTOMY DURING PREGNANCY

DURATION PREGNANCY	NO. CASES	ABORTION	END RESULT
1+	2	0	1 del. at term 1 unknown
2+	10	4 3-11-20-60 days	4 del. at term 2 unknown
3+	4	0	4 del. at term
4+	1	0	1 del. at term
5+	3	1 operative abort. (carcinoma)	2 del. at term
6+	1	0	1 del. at term
7+	2	0	2 del. at term
	23	5	15 del. at term 3 unknown

PATHOLOGY	
Dermoid	7
Simple serous	7
Corpus luteum	4
Pseudomucinous	2
Parovarian	1
Papillary serous cystadenoma	1
Papillary serous cystadenocarcin.	1
SYMPTOMS	
Present	11
Absent	12

was no maternal mortality but there were five abortions, one, an operative abortion in the fifth month, and four, all considered due to the celiotomy, in the first two to two and a half months. In considering this relatively high incidence of abortion of four* out of 22 cases, two factors must be considered. First, the role of the corpus luteum in maintaining pregnancy. Since it is generally accepted that this plays an insignificant part in maintaining pregnancy after the fourth month attention will be given in this series only to those appearing in the first trimester. In one of these four cases the corpus luteum was removed and abortion occurred on the eleventh postoperative day. In the remaining three, even though the corpus luteum was not disturbed, abortion occurred on the third, twentieth and sixtieth days after operation. In contrast to these there were three patients in whom the corpus luteum was removed but who did not abort. In this connection Andrews et al.[8] reported 13 cases in which bilateral dermoid cysts were removed during the first trimester, of which only two patients aborted. Thus, it seems justified to assume that the corpus luteum of pregnancy may not be essential to the maintenance of pregnancy at this time.

*One of these four patients was difficult to evaluate because she admitted attempting to induce an abortion prior to operation. Following oophorectomy she was discharged well but was readmitted four days later and aborted on what was actually her twentieth postoperative day.

The second important factor affecting the incidence of abortion involves the problem of the optimum time during pregnancy to subject a patient to oophorocystectomy. It will be noted that all postoperative abortions occurring in this series appear before the third month. Andrews et al.[8] in reviewing the literature from this point of view found the incidence of abortion to be lowest when these patients were operated upon during the fourth month, while the number that occur during the second month was relatively high. As judged from this series and the available literature,[9-13] the safest time during pregnancy to subject patients to oophorocystectomy is either during or after the fourth month.

It is evident from the study of these patients subjected to oophorocystectomy that the incidence of abortion was high, this untoward complication occurring in four out of 22 cases. It is possible that a certain number of these could have been avoided if operation had either not been performed at all or had been postponed until later in pregnancy. When these cases are compared to a similar group already referred to in the surgical cases (Table III), it is found that the acute surgical cases were all operated upon after the fourth month.

Although it may have been possible to postpone operation in some of these patients, fully half of them presented signs and symptoms of sufficient severity to indicate the possibility of torsion of the pedicle having taken place. In them anything but immediate operation would indeed have been hazardous. Furthermore, it is of interest to note that all of the abortions occurred in this half, while there were no abortions in those cases in which oophorocystectomy was performed merely as an elective procedure. In this connection it may be of interest to recall that any intraperitoneal irritation causing stimulation of the gastrointestinal tract may reflexly initiate uterine contractions. In explaining, therefore, why those patients with symptoms abort early in pregnancy, while those without do not, it appears logical that the peritoneal irritation occasioned by a partially ischemic ovarian cyst might well stimulate the uterus either directly or indirectly to empty itself. In none of these patients was progestin therapy routinely employed nor were any consistent efforts made to determine the pregnandiol excretion as has been advised by Nucci[14] and Andrews et al.[8]

An alternate method of course for dealing successfully with patients in whom the pregnancy is complicated by an ovarian tumor is indicated in Section B of Table IV. In all of these patients living babies were obtained by postponing operation till near term, at which time cesarean section was performed. In four cases the cyst was removed at this time, in one it was left in place.

In Table VII the microscopic diagnosis of the ovarian tumors removed is outlined. Seven of the tumors were dermoids, seven were simple serous cysts, two were pseudomucinous and one a parovarian cyst. There was one papillary serous cystadenoma, while in one instance both ovaries were removed for papillary serous cystadenocarcinoma. Four of these tumors measured approximately 6 cm. in diameter, while the other 19 were larger, the largest being 26 cm. in diameter. In one patient no attempt was made to remove a dermoid which was found firmly adherent to the pelvis.

The next group of interest is composed of eleven patients operated upon during the course of their pregnancy for myoma uteri. These are outlined in detail in Table VIII. In two patients exploration alone was performed, myomectomy being deemed inadvisable. Of these two,

TABLE VIII. MYOMECTOMY DURING PREGNANCY

OPERATION	NO. CASES	MONTH PREG.	ABORTED POST-OPERATIVELY	PATHOLOGY	DELIVERY AT TERM
Myomectomy	3	2 or less	3	Degeneration 2 Uncomplicated myoma 1	0
Myomectomy	2	2-4	0	Carneous degeneration	2
Myomectomy not feasible	2	2-4	2 One induced	———	0
Myomectomy	4	4-6	1	Degeneration cystic, hyaline or carneous	3
Total	11		6		5

one aborted postoperatively while the other was discharged well, only to be readmitted a week later having had an abortion induced shortly after leaving the hospital. In the nine patients in whom myomectomy was performed four aborted and five progressed to delivery at term. Myomectomy in this series, therefore, represents an operation, the fetal loss associated with which is exceedingly high.

The explanation for this large number of abortions lies in the excessive amount of uterine manipulation necessary to secure removal of the tumors. For instance, it was found that in those patients who progressed to term the size of the attachment of the myoma to the uterus was never over five centimeters in diameter. In those who aborted, however, the size of the attachment was so large that the uterus was of necessity severely traumatized during the course of the operation.

In studying these patients, therefore, from the point of view of postulating a therapeutic policy which in the future could be expected to result in a lower incidence of fetal loss, several factors immediately presented themselves. In the first place these eleven patients obviously belong to that large general group in which it is recognized that the pregnancy is complicated to a greater or lesser extent by the presence of a myoma of the uterus. It is true that most of these patients can be expected to progress to term without undue difficulty. There will, however, be a few who will present signs and symptoms due to the tumor which are of sufficient severity to make operation all but imperative. This situation presented itself in eight of the 11 patients. In the other three, however, the operative indications were unfortunately merely the presence of a large abdominal tumor unassociated with any real complaints upon the part of the patients themselves. Size alone therefore should not be accepted as a valid reason for operating upon such individuals. These experiences indicate that only those patients should be subjected to myomectomy who present very real and persistent complaints. Particularly is this true when it is appreciated that if the major ante-natal problem associated with the tumor concerns only its potential ability to obstruct the birth canal, cesarean section at term can be relied upon to yield living infants without undue risk to the mother. In this connection those cases have been reviewed in whom section was performed because of the obstructing effect of large myomata. This group of 22 patients is outlined in detail in section A of Table IX. It is interesting to note that all but two were elderly primiparas. There were no babies lost, but one mother, in whom the tumor was not removed, developed a fatal peritonitis.

As in the general surgical group there were a number of patients in this series in whom the preoperative diagnosis was incorrect. These 10 patients are outlined in Table X. In the first case the preoperative diag-

TABLE IX. CESAREAN SECTION

OPERATION	NO. CASES	PATHOLOGY	MATERNAL MORTALITY
A. INDICATION—MYOMATA			
Cesarean section and hysterectomy	7	Degeneration	0
Cesarean section and myomectomy	7	Degeneration	0
Cesarean section; tumor not removed	8	———	1 (Peritonitis)
B. INDICATION—OVARIAN			
Cesarean section Oophorocystectomy	4	Dermoid	0
Cesarean section Cyst not removed	1	Dermoid	0
	27		1

TABLE X. MISCELLANEOUS OPERATIONS DURING PREGNANCY

PREOPERATIVE DIAGNOSIS	NO. CASES	DIAGNOSIS AT OPERATION	MONTH OF PREGNANCY	END RESULT
Myomata utèri	1	Pregnancy	3	Delivered at term
Ectopic pregnancy	3	Pregnancy	1½	Delivered at term
Ectopic pregnancy	3	Incomplete abortion	1½-2	Abortion completed
Endometriosis	1	Pregnancy with adhesions	3	Delivered at term
Extens. adhesions	1	Extensive adhesions	5	Aborted first day
Myomata uteri missed abortion	1	Missed abortion	2 8 mos. amenorrhea	———

nosis was myomata uteri and a normal three months gravid uterus was observed at operation. In the next six cases in which the preoperative diagnosis was ectopic pregnancy, three of the patients were discovered to have a normal intrauterine gestation which progressed to term satisfactorily. In the other three the correct diagnosis was established as an incomplete abortion, all of these requiring a dilatation and curettage. The remaining three cases are self-explanatory. The significant find-

TABLE XI. HYSTEROMYOMECTOMY DURING PREGNANCY

INDICATION	NO. CASES	PATHOLOGY	MONTH OF PREGNANCY
Pregnancy not recognized	6	Uncomplicated myomata 5 Hyaline degeneration 1	Less than 7 weeks
Pregnancy suspected or known	4	Uncomplicated myomata	1½ to 2½ months
Renal disease	2	Uncomplicated myomata	2-3½ months

ing in this group of patients is that when a diagnosis of ectopic pregnancy cannot be made in any other way than by operation, simple exploration can be performed without incurring any excessive risk.*

Conclusions

Several conclusions of significance appear warranted from study of these patients.

1. Pregnant women tolerate even major surgical procedures quite as well as the nonpregnant.

2. When the surgical disease, however, becomes complicated by peritonitis, the outlook is unfavorable, and the maternal and fetal mortality, high.

3. Ovarian tumors complicating pregnancy may be removed with relative impunity provided operation can be postponed until after the first trimester.

4. Myomectomy should not be performed during pregnancy except upon urgent indications.

5. An exploratory celiotomy for suspected ectopic pregnancy may be performed with relatively little danger of interrupting a normal intrauterine pregnancy should the preoperative diagnosis fail to be substantiated.

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Discussion

DR. JAMES R. MILLER.—A number of years ago I reviewed the dermoid cysts seen at the Hartford Hospital. About every sixth patient had multiple dermoids. In one case which necessitated the removal of one ovary entirely because of torsion, the corpus luteum of pregnancy in the other ovary lay between two other dermoid cysts. It was possible to shell the dermoids out by careful dissection. The patient went to term and was delivered of a live baby.

Recently in the Hartford Hospital, we had a patient, six months pregnant, who had had a previous gynecologic operation. She had partial and then complete obstruction over a period of about seven days. About three feet of bowel were resected and an ileostomy was done, which was closed later. She also went to term.

*Although not strictly relevant to the topics discussed in this paper 12 patients in whom hysteromyomectomy was performed during pregnancy are outlined in Table XI. They are included here fore the sake of completeness, although actually they did not constitute a surgical complication during pregnancy. The pregnancy was terminated by the very nature of the operation.

DR. MORTIMER D. SPEISER.—At the French Hospital there have been five cases of acute intestinal obstruction complicating pregnancy in the first 6,822 obstetric admissions. Four of the cases followed a previous laparotomy, one for multiple myomectomy, another for an appendectomy and Baldy-Webster suspension, and two for a simple appendectomy without drainage. The fifth case, without a previous history of a laparotomy or pelvic inflammatory disease, was due to a volvulus of the sigmoid.

Unfortunately, when the classical symptoms of ileus arise during the course of a pregnancy they do not always receive the serious consideration which they merit. The periodic cramplike pains are frequently considered to be the result of uterine rather than intestinal contractions. The painful sensation should be synchronous with palpable uterine contractions if the uterus is palpable above the symphysis. Nausea and vomiting may occur at any time during the course of pregnancy, but it is especially significant that it is most prevalent during the first trimester of pregnancy when intestinal obstruction is least common. Constipation is very frequent in the female and almost universal during pregnancy, but if in addition to this, repeated enemas are ineffectual and do not relieve the pain and distention, acute intestinal obstruction must be considered. Furthermore, rapidly increasing tympanitic abdominal distention, with pain and obstipation, must have some mechanical basis. For confirmation one may resort to roentgenologic studies. The characteristic picture of small bowel obstruction is sufficiently pathognomonic, but the absence of such findings cannot be interpreted as ruling out this complication. The use of a Miller-Abbott tube may be a distinct aid to such a diagnosis. Again, large bowel obstruction is readily visualized on roentgenographic studies with the use of a barium enema if necessary.

As the result of early diagnosis followed by adequate preoperative and operative care, there was no maternal mortality in our five cases. In four of the patients it was necessary to do an hysterotomy in order to explore the abdominal contents adequately. This procedure, unfortunately, accounted for three fetal deaths due to prematurity. In only one instance, which occurred in a pregnancy of three and one-half months' gestation, were we able to leave the uterus unmolested.

DR. WILLIAM E. STUDDIFORD.—I did not hear Dr. Child say anything particular in regard to the site of the incision for appendectomy during pregnancy. I had difficulty in approaching the appendix with an eight months' pregnancy obstructing the operative field. In the particular case to which I have referred, we used a muscle-splitting incision, the center of which was about halfway between the anterorsuperior spine and the costal margin. With this incision the top of the right broad ligament came into view and the uterus lay just to the left. With a deep right-angled retractor, it was possible to pull the broad ligament down and the uterus to one side, bringing the appendix into view. It was removed then without any difficulty.

DR. SAMUEL A. COSGROVE.—Our incidence of these surgical complications of pregnancy has not been as high as those at the Lying-in Hospital. At the Margaret Hague Maternity we have had 29 cases of acute appendicitis, several of which were characterized by gangrene or rupture of the organ, five by generalized peritonitis. Twenty-four occurred before the seventh month; five beyond the seventh month and two were actually intrapartum.

In 13 other cases the appendix was removed during pregnancy. These were removed either when associated with other pathology or some as a result of error in diagnosis. Of this total of 42 cases one mother died, a late case of generalized peritonitis, giving a mortality rate of 4.2 per cent. Five fetuses were lost, two of which were inevitably compromised before operation, a mortality of 12 per cent.

Our number of ovarian cysts and fibromas has not been as large as the Lying-in Hospital series, perhaps because of a little more conservative tendency on our part. We have had 17 cases of ovarian and parovarian cysts, with no maternal mortality, but with 41.2 per cent fetal loss. This is comparable to that of Dr. Child and Dr.

Douglas. There were 10 cases of uterine fibroids, with no maternal mortality, but with a 60 per cent fetal loss, which is comparable to theirs.

We had six cases of thyroidectomy, with no maternal or fetal loss.

We do not feel that the difficulty of diagnosis is greater in the pregnant than in the nonpregnant. About the only specific diagnostic evidence that one can depend upon in estimating acute appendicitis is localized, persistent tenderness. We have not found so much dislocation of the area of tenderness as other observers have and we feel that we can make a reasonably sure diagnosis of appendicitis without depending on a triad or any other combination or syndrome which so often does not exist. The operation itself is not serious, as has been demonstrated by the results which have been reported here this evening. Just the other day we had a patient who delivered a seven months' fetus four days after an appendectomy for an acute catarrhal appendicitis. The wound does not apparently suffer any particular stress; there is no more danger of dehiscence because the woman goes into labor immediately or a short time after operation than under any other circumstances. Therefore, in view of the well-taken point that in late pregnancy the progress of acute appendicitis may be more malign and rapid than it is in the nonpregnant, it is just as appropriate to operate on a few of these cases on suspicion as if a similar situation occurred in the nonpregnant woman.

There is one type of case in which I would recommend conservatism in acute appendicitis and it may be the answer to part of our mortality. That is the advanced case of general peritonitis. Some of those cases are, from a surgical viewpoint, not operable and do better if treated conservatively. This is hardly the place to develop that thesis, but I would commend to your attention the very occasional case which will do better on a strict Ochsner regimen and entire dependence, for a considerable period of time if necessary, on parenteral maintenance of water, electrolyte and protein balance.

DR. GEORGE W. KOSMAK.—I would like to ask Dr. Douglas if they encountered among these surgical complications any ureteral calculi. I remember one case at the Lying-in Hospital many years ago where the patient had a ureteral calculus on the right side, causing obstruction and giving rise to symptoms very similar to an appendicitis. The patient was operated upon and a calculus about one inch long taken from the ureter in the seventh month of pregnancy. The patient went on to full term.

DR. ALFRED C. BECK.—For a number of years we have been very conservative at the Long Island College Hospital in the treatment of fibroids complicating pregnancy. Formerly in Doctor Polak's time some myomectomies were done. During the past ten years, however, I cannot recall a single case in which we thought myomectomy was necessary. Occasionally these tumors become very painful but they respond to conservative treatment.

If a cesarean section is necessary for obstruction due to a fibroid in the lower uterine segment, we believe that the fibroid should not be left behind. The cesarean section accordingly should be followed by hysterectomy or the tumor should be removed by myomectomy. Otherwise a tumor which is large enough to interfere with the passage of the child will interfere with drainage from the uterus and consequently lead to subsequent difficulty.

DR. CHILD (closing).—Intraperitoneal drainage is instituted in all cases of acute appendicitis in which free perforation has taken place. Occasionally, in cases of gangrenous appendicitis without perforation the parietal wall alone is drained, that is, down to the peritoneum. In the four cases in this series in which generalized peritonitis was present drainage was instituted.

In all cases in which appendicitis was suspected the peritoneal cavity was entered through a McBurney type of incision. The midpoint of this incision is usually placed over the point of maximum tenderness. The advantages of this type of incision, particularly if perforation has taken place, are too well known to require repe-

tition here. If, on the other hand, the preoperative diagnosis is found to be incorrect and one of the rectus incisions is needed, the additional trauma of the McBurney incision is not considered particularly detrimental to the patient.

The so-called Ochsner form of treatment is not customarily employed at the New York Hospital. This does not mean, however, that a reasonable amount of time is not allowed to prepare adequately an acutely ill patient for operation.

We have not encountered any patients in whom a right renal calculus was mistaken for acute appendicitis.

DR. DOUGLAS (closing).—Dr. Bishop's question with relation to the incidence of myomectomy at the present time as compared to former experience is difficult to prove statistically in a small series of cases. It is my impression that we are interfering less frequently now than formerly. Actually only one case has been operated on since 1939. I was interested in hearing Dr. Beck say that they have not had occasion to perform a myomectomy recently. I have reviewed one of Dr. Polak's papers on the subject and the incidence of myomectomy was obviously higher then than it is at this time.

In regard to Dr. Kosmak's question with reference to ureteral calculi, there was a considerable number of patients with this complication who were not subjected to operation during pregnancy and who are not included in this study.

Kloman, Erasmus H.: Vesicovaginal Fistula, South. M. J. 34: 271, 1941.

The author briefly reviews the history of operations for the cure of vesicovaginal fistula, indicating the significant contributions to the procedure in the successive stages of its development. Modern technique, it is emphasized, is based upon the work of pioneer surgeons. He makes the distinction between "present-day" gynecologic fistulas, which result from pelvic operations, the use of radium, and the cautery, and obstetric fistulas which develop consequent to the trauma of labor and parturition. The postoperative fistulas contrast with the latter in that they are usually high in the vaginal vault and of difficult access. Accordingly, the author employs the knee-chest posture for this operation, stressing the advantages of better exposure of the operative field, with the surgeon working down upon the latter rather than up under the pubic rami, decreased vascularity and relative anemia of the elevated tissues.

The patient is anesthetized in the usual dorsal position, then turned to the prone position and elevated to the knee-chest posture by a special device which may be adapted to any operating table. This position may be maintained indefinitely. A method whereby the fistula may be drawn down closer to the introitus in order that its dissection and repair may be facilitated, is an original contribution of the author. This is accomplished by the use of 6 to 8 traction sutures of stainless steel wire which are introduced through the vaginal mucosa and submucosa about 2 cm. from the periphery of the fistula orifice, and held with clamps. The method obviates the necessity for using metal retractors which may offer obstruction. Preliminary to operation, any existing urinary tract infection must be cleared. The relationship of the fistula to the urethra and the ureters should be determined; if the proximity of the ureteral orifice is close, a catheter may be passed, or transplantation of the ureter performed.

Complete separation of the vaginal mucosa and the bladder is essential so that the closure may be accomplished with a minimum of tension. For the vesical wall a purse-string catgut suture reinforced by a second layer of continuous suture is employed. Apposition of the vaginal flaps is accomplished with nonabsorbable fine dermal sutures which remain four weeks. Postoperatively, the patient is placed in a prone position and a self-retaining urethral catheter provides for bladder drainage and for twice daily irrigation. Acidification of the urine tends to prevent crust deposits.

ARNOLD GOLDBERGER.

CARCINOMA OF THE CERVIX COINCIDENT WITH PREGNANCY*

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THE literature dealing with carcinoma of the cervix coincident with pregnancy consists for the most part of reports of a single case or of statistics assembled by a number of authors from these reports. There is little agreement concerning frequency, behavior, treatment or the prognosis of carcinoma associated with pregnancy.

Material

This study was made to determine as accurately as possible the incidence of pregnancy in approximately 3,500 cases of carcinoma of the cervix observed at the Mayo Clinic in nearly thirty-two years, that is from July 1, 1909 to February 28, 1941, inclusive, and to ascertain whether or not the prognosis of the disease is modified by the coexistent pregnancy. It was considered of interest to investigate the possibility that gestation may occur in the presence of an established carcinoma of the cervix. The results of therapy were reviewed in an effort to determine the method or methods of choice in the treatment of carcinoma of the cervix coincident with pregnancy.

In twenty-six, or 0.7 per cent, of the 3,570 cases of carcinoma of the cervix, the patients also were pregnant. In forty-five other cases there was a close association between pregnancy and carcinoma of the cervix but the coexistence of these two conditions could not be proved absolutely; therefore, these cases were excluded from consideration. We shall attempt to correlate the findings in these twenty-six cases with the findings in the cases reported in the literature.

Incidence

In the reports in the literature, the stated incidence of carcinoma of the cervix among pregnant women has varied. However, examination of a number of such reports indicates that the incidence is in the neighborhood of 0.05 per cent. Thus, when one considers the frequency of pregnancy, a complicating carcinoma of the cervix is not an extremely rare occurrence.

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‡The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

TABLE I

CLINICAL AND PATHOLOGIC FINDINGS, TREATMENT AND RESULTS

CASE	YEAR OF OBSERVATION	AGE YEARS	GRAVIDA	PARA	STAGE OF PREGNANCY	MALIGNANT LESION		GRADE	DURATION OF SYMPTOMS	TREATMENT	RESULTS, INTERVAL AFTER TREATMENT	
						TYPE	STAGE				ALIVE	DIED
1	1909	33	5	3	Term	No report	4		4 mo.	Porro's cesarean operation; subtotal hysterectomy		3 days
2	1912	31	8	4	Term	Squamous cell epithelioma	2	4	5 mo.	Cesarean section; total abdominal hysterectomy		9 mo.
3	1915	33	5	2	30 wk.	Squamous cell epithelioma	2	3	6 mo.	Total abdominal hysterectomy	23 yr.	
4	1916	36	5	5	Term	Squamous cell epithelioma; adenocarcinoma	2	3	Postpartum	Vaginal hysterectomy		15 mo.
5	1916	35	7	5	16 wk.	Squamous cell epithelioma	2		9 mo.	Radium and roentgen therapy		8 mo.
6	1916	40	8	8	Term	Squamous cell epithelioma	3		6 mo.	Radium and roentgen therapy		8 mo.
7	1917	34	11	3	6 wk.	Squamous cell epithelioma	1	4	7 mo.	Vaginal hysterectomy; radium and roentgen therapy	12 yr.	
8	1918	35	2	1	18 wk.	Squamous cell epithelioma	4	3	2 yr.	Total hysterectomy; radium and roentgen therapy		6 yr.
9	1919	37	11	11	Term		3		2 mo.	Porro's cesarean operation; radium therapy		4 mo.
10	1919	28	7	5	18 wk.	Squamous cell epithelioma	2	4	5 mo.	Total abdominal hysterectomy; radium therapy		4 mo.
11	1919	26	5	4	Term	Squamous cell epithelioma	1	4	1 yr.	Vaginal hysterectomy; radium and roentgen therapy		2 yr.

12	1920	29	5	4	32 wk.	Squamous cell epithelioma	4	3	4 mo.	Cesarean section; subtotal hysterectomy; radium and roentgen therapy		1 wk.
13	1922	28	4	3	25 wk.	Myxosarcoma*	1	3	1 yr.	Subtotal hysterectomy		1 yr.
14	1928	32	2	1	10 wk.	Squamous cell epithelioma	3	3	6 mo.	Radium and roentgen therapy	11 yr.	
15	1928	39	13	11	6 wk.	Adenocarcinoma	2	2	1 yr.	Total abdominal hysterectomy; radium and roentgen therapy	10 yr.	
16	1928	27	5	4	18 wk.	Squamous cell epithelioma	2	4	2 mo.	Total abdominal hysterectomy; radium and roentgen therapy	11 yr.	
17	1928	34	7	2	16 wk.	Squamous cell epithelioma	1	4	6 mo.	Total abdominal hysterectomy; radium and roentgen therapy	11 yr.	
18	1932	27	2	1	Term	Squamous cell epithelioma	4	3	2 mo.	Radium therapy		5 mo.
19	1932	32	2	2	Term	Squamous cell epithelioma	3	3	9 mo.	Radium and roentgen therapy		10 mo.
20	1934	28	3	2	20 wk.	Squamous cell epithelioma	3	4	1 yr.	Cesarean section; radium and roentgen therapy		22 mo.
21	1936	35	1	0	8 wk.	Adenocarcinoma	1	2	0	Total abdominal hysterectomy; radium and roentgen therapy	2 yr.	
22	1937	34	7	3	27 wk.	Adenocarcinoma	1	1	1½ yr.	Wertheim's operation (1939); radium and roentgen therapy	2½ yr.	
23	1939	26	3	1	15 wk.	Squamous cell epithelioma	3	3	6 mo.	Radium and roentgen therapy	Not traced	
24	1939	31	2	2	Term	Squamous cell epithelioma	2	3	14 mo.	Porro's cesarean operation; subtotal hysterectomy; radium and roentgen therapy	1 yr.	
25	1940	25	3	2	10 wk.	Squamous cell epithelioma	2	4	3 mo.	Wertheim's operation; radium and roentgen therapy	5 mo.	
26	1941	41	9	6	14 wk.	Squamous cell epithelioma	1	4	1 yr.	Wertheim's operation; radium and roentgen therapy	2 mo.	

*This paper deals prevailingly with carcinomas; this one case of myxosarcoma was not excluded from the series.

As an incidental finding in cases of carcinoma of the cervix, on the other hand, pregnancy occurs with surprising frequency. Incidences of from 0.3 to 5.1 per cent have been given by various authors. The experience of most men, however, would agree to an incidence of about 1.5 per cent. As previously stated, pregnancy also was present in twenty-six, or 0.7 per cent, of 3,570 cases of carcinoma of the cervix observed at the clinic. Since all of these patients came to the clinic because of carcinoma of the cervix and not because of pregnancy, this percentage does not indicate the true incidence of carcinoma of the cervix among pregnant women. In the years 1910 to 1941, inclusive, 8,500 women registered at the clinic because of pregnancy and carcinoma of the cervix was not observed in any of these women.

Age of Patients

The youngest patient in our series of twenty-six cases was twenty-five years of age and the oldest was forty-one years of age (Table I). There appears to be very little predilection for carcinoma of the cervix coincident with pregnancy to occur at any particular age since there were almost equal numbers of patients in each five-year age group. The average age of the patients was 32 years. The average time at which the carcinoma of the cervix was discovered was in the twenty-fourth week of pregnancy.

Gravidity

In only one instance did carcinoma occur in the first pregnancy; in five cases it was discovered in the course of the second pregnancy. The greatest number of pregnancies in any one case was thirteen (Table I). In the entire group of cases the average number of pregnances was 6 and the average number of children was 4.

It has been stated that pregnancy may supervene in a case of established carcinoma of the cervix. In three cases in this series, the pregnancy almost certainly occurred after carcinoma of the cervix was present; in a fourth case, there was definite proof that the carcinoma antedated the pregnancy. In case 14, carcinoma stage 3 was discovered in the tenth week of pregnancy. It is reasonable to suppose that carcinoma of such an advanced stage had been present much longer than ten weeks and that the pregnancy occurred after the carcinoma was well established. A similar reasoning may be applied in case 15, in which carcinoma stage 2 was found in the sixth week of pregnancy. This was the earliest stage of pregnancy at which carcinoma was discovered in this series of cases.

In another case bleeding from the cervix occurred in the eighth month of pregnancy, in December, 1920. The patient had been told that she had a "slight growth on the cervix." A few weeks later, growths protruded from the vagina and there was much foul, bloody discharge. In May, 1921, polyps were removed, only to return four months later; they

were removed again in October, 1921. When the patient first was seen at the clinic in February, 1922, fourteen months after the discovery of the tumor, she again was pregnant; at this time she was in the fifth month of pregnancy. She had a large cervical tumor which proved to be a myxosarcoma grade 3. Undoubtedly these recurring tumors were myxosarcomas and she twice became pregnant during the course of the disease.

Definite proof that carcinoma may antedate conception is furnished by case 22. In October, 1937, the patient aborted a fetus of about one month. Curettage was performed and a biopsy disclosed carcinoma of the cervix. In June, 1938, she was re-examined and radium therapy was prescribed. In July, 1938, biopsy of a large section of the cervix again disclosed papillary adenocarcinoma. In September, 1938, about a year after biopsy first had disclosed carcinoma, she again became pregnant.

Symptoms

The symptoms of carcinoma of the cervix coincident with pregnancy are those of carcinoma of the cervix plus the symptoms of pregnancy. All authors agree that vaginal hemorrhage is the most common symptom of carcinoma of the cervix. The bleeding may consist only of postcoital spotting. On the other hand, it may not be associated with trauma and may be profuse. An aqueous, odorous discharge commonly is a late symptom. Bleeding was the initial symptom in twenty-three, or 88 per cent, of the twenty-six cases in this series. In most of the cases the patients had had symptoms for two to six months before the diagnosis was made; three patients had not had any symptoms. The average duration of symptoms was 7 months. In one case abnormal bleeding had occurred for one year and in another case it had occurred for two years.

Gross, as well as other authors, found that the duration of symptoms of carcinoma of the cervix was shorter in cases in which the women were pregnant than it was in cases in which the patients were not pregnant. In a series of cases reported by this author, the duration of symptoms was as follows: three months in cases in which the patients were pregnant and 8 months in cases in which the patients were not pregnant. In almost a fifth of the reported cases the symptoms of carcinoma antedated pregnancy.

Diagnosis

We agree with Rochet's statement that the diagnosis of carcinoma of the cervix coincident with pregnancy often is missed because of the fear of making a pelvic examination during pregnancy. He urged the making of a pelvic examination in any case in which a malignant lesion of the cervix is suspected. He also recommended biopsy and said that this

procedure is associated with little risk even in cases in which the patients are pregnant.

The literature contains reports of several cases in which carcinoma of the cervix has been mistaken for threatened abortion or placenta previa. Carcinoma of the cervix is more likely to bleed as the result of trauma whereas in cases of placenta previa profuse bleeding occurs without apparent provocation. Carcinoma of the cervix is hard and indurated while the cervix of the normal pregnant uterus is soft and velvety.

At this point it perhaps might be advisable to mention the possibility of confusing carcinoma with the hypertrophic changes in the cervix of a pregnant uterus. Clinically, in the presence of pregnancy, the cervix may on occasion appear sufficiently abnormal to cause one to suspect the presence of a malignant lesion. An experienced pathologist would recognize the histologic appearance of tissue obtained by biopsy from the cervix in a case of normal pregnancy as opposed to that of carcinoma.

Treatment

Previous to 1880, the treatment of carcinoma of the cervix associated with pregnancy was purely symptomatic. The pregnancy was allowed to go to term; artificial methods of delivery were used only in cases of arrested progress. Then cautery, local excision of the obstructing tumor, multiple cervical incisions, manual dilatation, version and extraction, or forceps delivery became the procedures usually employed.

In 1881, Spencer Wells did the first hysterectomy for carcinoma of a known pregnant uterus. By 1909, the year Williams published his excellent article on the subject, several choices of operation were possible. About 1910, when abdominal hysterectomy had become comparatively safe, the radical operation of Wertheim, with or without cesarean section, became the method of choice in cases in which the lesion was operable.

Surgical Treatment.—In nine of the thirteen cases observed in the years 1909 to 1927, inclusive, the cervical lesion was considered operable, stages 1 or 2, when the patients first were observed. Radical operation was performed in seven of the nine cases; total hysterectomy was performed in one of these cases (Case 8) two years before admission to the clinic. In three of the eight cases the patients were in an advanced stage of pregnancy, which ordinarily makes the prognosis poor. Of the seven patients, only two remained free of recurrence.

The cervical lesion was found to be operable in eight of the thirteen cases that were observed in the years 1928 to 1941, inclusive. Total hysterectomy was employed in seven of the eight cases. When the seven patients last were heard from, all of them were living; however, only three of the patients had been followed for five or more years after operation.

Cesarean section was performed in six cases. In four of these cases it was followed by subtotal hysterectomy and in another case by total hysterectomy. Although irradiation also was used in four of the six cases the results were not good. The lesions were well advanced at the time of operation and none of the patients lived for five years after the operation.

Total abdominal hysterectomy was performed in eleven cases (Cases 2, 3, 8, 10, 15, 16, 17, 21, 22, 25 and 26). In seven of these cases, more than ten years have elapsed since the operation was performed. In four of the seven cases, the patients were alive when this paper was written; therefore, the ten-year survival rate in the seven cases was 57 per cent; this figure represents the survival rate in cases in which the stage of growth permitted radical operation.

The technique of the Wertheim operation was employed in nearly all of the total hysterectomies, and in three cases (Cases 22, 25 and 26), which were observed more recently the operation was defined as a Wertheim hysterectomy. Although the results so far have been good in these three cases, the time that has elapsed since operation was performed is not sufficient to permit one to say that the patients probably have been cured.

Vaginal hysterectomy was performed in three cases (Cases 4, 7 and 11). In one case it apparently effected a cure.

In the first few cases in this series, the actual cautery was applied to the malignant lesion before the uterus was removed; however, this procedure apparently was of little benefit.

Irradiation Therapy.—With the advent of roentgen therapy, opinion became divided as to the relative value of surgical and nonsurgical treatment. Since there was some hope of obtaining a viable infant in cases in which roentgen therapy was employed, personal and religious sentiments in this regard became manifest. The French literature, especially, favored preservation of the fetus by using roentgen therapy until the viability of the fetus was assured.

Irradiation therapy frequently has been used in an attempt to control the growth of the carcinoma until the child has become viable. This is not without risk to both mother and child. Murphy (Schmitt), and other authors have revealed that abortion occurs in about 24 per cent of cases in which this type of therapy is used and that in about 24 per cent of the remaining cases the offspring are defective; about half of the defective infants are microcephalic idiots. This predominance of microcephalic idiocy has been a constant finding among irradiated fetuses. A child often is reported apparently normal at birth, but a follow-up study frequently shows that it died soon afterward, or that after a lapse of from four to seven years its faulty development became manifest.

The importance of this sequel to irradiation during pregnancy has assumed medicolegal significance. Recently, an adverse decision was rendered in suit for damages against a physician because a microcephalic idiot was born to a woman whom he had irradiated early in the course of pregnancy. The pregnancy had not been recognized until after irradiation had been employed.

Rev. P. A. Finney and other moral theologians agreed that, as long as the treatment is directed primarily against the carcinoma which threatens the mother's life, the death of the fetus is secondary and indirect. The church condones the removal of the pregnant uterus for carcinoma of the cervix. In spite of the prevalence of this sound opinion, treatment in many instances is influenced by personal or religious interpretation.

The majority opinion of the past fifteen years favors, when possible, immediate radical removal of the uterus and the subsequent use of irradiation therapy. The results of operation performed in the course of pregnancy are more satisfactory than are the results of operation done after delivery. Nearly all authors agree that vaginal delivery of the fetus increases the immediate mortality of both mother and child and that the ultimate prognosis is likewise made worse.

Irradiation was not employed in the first three cases of this series as these cases were observed prior to 1916, that is before irradiation was widely used either alone or in conjunction with operation in the treatment of carcinoma.

Radium was the principal therapeutic agent employed in ten cases (Cases 5, 6, 9, 12, 14, 18, 19, 20, 23 and 24). In two of these cases (Cases 9 and 24), Porro's operation preceded radium therapy and two other cases (Cases 12 and 20) radium therapy was employed after cesarean section was performed. No surgical operation was performed in the remaining six cases. The lesion was considered operable in only one of these six cases, namely, Case 5. The fact that the patient in this one case died cannot be used to condemn the use of irradiation in the treatment of carcinoma of the cervix coincident with pregnancy. In one of the six cases (Case 14), more than eleven years have elapsed since the patient was treated and there has been no recurrence of the carcinoma. In this case, the carcinoma was classified as stage 3.

In two cases (Cases 23 and 24) which were observed recently, the lesion has not responded well to irradiation therapy. In one case (Case 23) the disease was progressing rapidly when the last follow-up was obtained. In the other case (Case 24), the carcinoma was in a rather early stage of development when the patient first was seen at the clinic but it progressed rapidly to stage 4 while the patient was undergoing treatment. The later use of roentgen therapy produced some symptomatic improvement.

Abortion occurred in all cases in which irradiation was applied to the pregnant uterus. In five of the cases, irradiation therapy was begun in the post-partum period. Vaginal or cesarean delivery had resulted in a living child in all of these cases. In four of the five cases, the mothers died of carcinoma; in the remaining case, the lesion was progressing rapidly when follow-up data last were obtained.

In seven of the ten cases in which irradiation was employed, roentgen therapy was used in conjunction with radium therapy. In two of the three cases in which roentgen therapy was not employed (Cases 9 and 10), the patients refused to undergo further treatment; in the remaining case (Case 18), it was felt that only palliative radium therapy was justified.

Results and Prognosis

In twelve of the twenty-six cases, the patients were alive when the last follow-up data were obtained; however, in six of these cases, the patients have not been followed for five years. In two of these six cases, the disease apparently has made considerable progress and the prognosis was considered unfavorable when the last follow-up data were obtained. In the remaining four cases, the patients apparently were free of recurrence of the lesion, two and a half years, two years, five months, and two months respectively after they were dismissed from the clinic.

In twenty cases, at least five years have elapsed since the patients were treated at the clinic. Of these twenty patients, six were living and fourteen were dead when the last data were obtained. One of the patients died of an accidental injury but she had no recurrence of the carcinoma for two years after she was treated at the clinic. Thirteen patients died of extension of the malignant lesion. One patient lived six years but had a recurrence of the lesion before five years had elapsed. Of the patients who are alive, one has lived for twenty-three years after treatment, one has lived for twelve years, three have lived for eleven years and one has lived for ten years, without evident recurrence. A cure apparently was obtained in six, or 30 per cent, of the cases in which the patients have been followed for five or more years. If the case in which the patient died accidentally were omitted from these twenty cases, this percentage would be increased to 32.

Effect of Pregnancy on Carcinoma.—Whether carcinoma is stimulated, retarded, or unaffected by the coexistent pregnancy is a subject of dispute. There are well-substantiated reports which reveal tremendous acceleration in the growth of the carcinoma; others equally verified have demonstrated a marked inhibitory effect on the progress of the malignant lesion.

The cause of the rapid progress of the carcinoma is not known. It has been suggested that an increase in metabolism, hypercholesteremia, hyperemia, increased amount of glycogen in the cells, "looseness of tissue,"

or increased lymph supply consequent to pregnancy favor the growth and dissemination of the carcinoma. Cervical lacerations attendant on parturition are generally conceded to encourage a rapid spread of the carcinoma.

Gross and Zweifel, quoted by Bainbridge, early in their experience expressed the opinion that pregnancy accelerated the growth of carcinoma but they later changed their opinion to affirm the retarding effect of pregnancy upon carcinoma. Peller was able to demonstrate that in cases of carcinoma of the cervix in which the patients are of equal age the mortality rate is lower in cases in which the patients are pregnant or in the puerperium than it is in the cases in which the women are not pregnant. Bowing showed a significantly better prognosis for women who had been pregnant. Twenty-seven and seven-tenths per cent of women who had been pregnant obtained good results from therapy while the five-year survival rate was only 20.6 per cent for women who had never been pregnant.

Emge's experience with six pregnant patients indicated that the chance of cure of cervical carcinoma coincident with pregnancy was increased above the average.

Stöckl expressed the opinion of many authors in so far as he found no significant alteration in the behavior of carcinoma because of pregnancy, although he recognized individual cases in which the growth of the lesion was apparently stimulated or retarded.

In this connection the work of Slye is most interesting. She observed that when female mice were constantly pregnant energy was withheld from the tumor, which then grew with extreme slowness. If, however, there was an interval between pregnancies, or a termination of pregnancy, the energy which was running into reproduction was released and diverted into the tumor, which then grew more rapidly. During the six or eight days a female mouse is nonreproductive, the tumor grows much more rapidly than it does during the total eight months or a year that she is reproductive. If the tumor antedates the impregnation considerably, the currents of energy are with difficulty diverted to the pregnancy, and probably never wholly so. Hence, when the tumor growth is well advanced before impregnation, rarely are any offspring born; when offspring are delivered, they are likely to be small and undernourished and are rarely suckled.

Effect of Carcinoma on Pregnancy.—Sterility, on the basis of a coexistent endometritis, is generally considered to prevail in cases of carcinoma of the cervix. However, the presence of carcinoma of the cervix does not preclude the possibility of a subsequent pregnancy. Even a second pregnancy during the course of development of carcinoma of the cervix has been reported several times, and Basden collected twelve reported cases in which conception occurred after irradiation therapy.

If the carcinoma is untreated and if the pregnancy is allowed to continue, the pregnancy will proceed to full term in about two-thirds of the cases, but only a third of the infants will survive delivery by the vaginal route.

The child of a carcinomatous mother is not likely to be retarded or below normal viability unless the mother is cachectic. The experimental work of Slye supports this opinion.

In fifteen of the twenty-six cases, the pregnancy terminated prior to viability of the fetus. Spontaneous abortion occurred in one of the fifteen cases; in the remaining fourteen cases, the pregnancy was terminated by surgical intervention or irradiation therapy. In two of the eleven cases in which the fetus was viable, a premature infant was delivered in the course of a surgical procedure; in the remaining nine cases, pregnancy progressed to full term.

Of the six patients who lived ten years or more, three were in the first trimester of pregnancy when the carcinoma first was discovered, two were in the second trimester, and one had just entered the third trimester. None of the patients who carried the fetus to or nearly to term lived more than two years. When the diagnosis of carcinoma was made, the pregnancy had reached term in only one, or 14 per cent, of the seven cases in which the lesions were classified as stage 1. When the diagnosis was made, the pregnancy was at or near term in three, or 33 per cent, of the nine cases in which the lesion was stage 2, in three, or 50 per cent, of the six cases in which the lesion was stage 3, and in three, or 75 per cent, of the four cases in which the lesion was stage 4. Although the number of cases in this series is small, these figures strongly suggest that carcinoma of the cervix becomes progressively more severe as pregnancy advances. The number of pregnancies did not influence the prognosis. In cases in which the patients lived ten or more years, the average number of pregnancies was seven, which corresponds closely with the average number of pregnancies in the entire series of cases.

Fetal Prognosis.—According to Danforth, Cornil reported the only case in which carcinoma is known to have affected the fetus directly. In this case, metastatic lesions were found in the frontal bone, patella, peritoneum and thyroid gland of the fetus.

The medical literature of the last quarter of the nineteenth century contains reports of several cases in which the fate of the fetus was studied. In these early reports, no radical treatment was employed; consequently, the pregnancy was not interfered with. In a third of the cases reported by Cohnstein, the pregnancy terminated in premature delivery or abortion; in two-thirds of the cases in which the pregnancy was permitted to continue to term, the infants were born dead or died shortly after birth. The experience of Theilhaber and Van der Veer were similar. For many years, however, treatment has not been directed so much at saving the fetus as it has been at controlling the carcinoma. Cesarean section now offers the same excellent chance for a viable fetus as it does in certain other obstetric conditions.

In those cases collected by Strauss, in which an attempt was made to control the lesion by irradiation and at the same time secure a living

child, only 37 per cent of the pregnancies progressed to term and in 18 per cent of these cases children proved to be microcephalic idiots.

Maternal Prognosis.—Prior to the end of the last century, the woman with carcinoma of the cervix was almost certainly expected to die. This was true regardless of a complicating pregnancy; only very rarely did the carcinoma respond to local measures. The addition of pregnancy to the disease merely hastened the inevitable end. The immediate mortality was high; 40 per cent to 60 per cent of the mothers failed to survive delivery.

The surgical approach to the disease improved matters considerably. In 24 to 30 per cent of cases in which radical hysterectomy was employed, the patients were alive five years later. By 1910, cesarean section had cut the immediate maternal mortality to 22 per cent. In fifty cases collected by Pankow, the operability rate was 92 per cent and the five-year survival rate was 42 per cent. Of six patients treated at the Stanford University Hospital five have lived five years or more after their dismissal. Two were treated by hysterectomy and the remainder by irradiation.

Many authors feel that the rate of operability is higher in the presence of pregnancy and that the prognosis is no worse when pregnancy is present than it is when pregnancy is not present. It has been a common opinion that young women with cervical carcinoma do less well than do older women, and the experience of Neill tends to support this view. However, Bowing, in a recent review of 1,491 cases of cervical carcinoma, was more encouraging as he found that young women have only a slightly poorer prognosis than do older women. In our series of twenty-six cases, we did not find any definite relationship between the age of the patients and the extension of the lesion or between the age of the patients and the period of survival.

Family History.—The family history in this series of cases is most interesting. Seven, or 35 per cent, of the twenty patients who were observed five or more years prior to 1941 gave a family history of carcinoma. Fourteen of the twenty patients are dead; all died of carcinoma except one (Case 11), who died as a result of an accident. All but one of the living patients gave a family history of carcinoma. Since five of the seven patients who gave a family history of carcinoma obtained at least ten-year cures, one might be tempted to offer the hypothesis that such patients were "cancer conscious" and would be likely to seek treatment early in the course of their disease. Investigation showed that this reasoning does not hold true. In one case a large carcinoma of the cervix was discovered on the third post-partum day when an attempt was made to control persistent hemorrhage. In another case, the carcinoma was discovered two months after symptoms developed, but in the remaining cases, symptoms had been present for five to twelve months before the diagnosis was made. In these cases, the patients did

not obtain diagnosis and treatment any earlier than do patients with a completely negative family history and we are at a loss to explain the cause for the more favorable results in cases in which there was a family history of carcinoma.

Stage of Lesion.—In five of the seven cases in which the lesion was classified as stage 1*, the patients were alive when follow-up data were last obtained; however, in three of these cases, less than five years had elapsed since the patients were treated at the clinic. Two, or 50 per cent, of the remaining four patients were alive when the last follow-up data were obtained.

The lesion was classified as stage 2 in nine cases. When the last report was received, five of the nine patients were living. In seven of the nine cases, ten or more years had elapsed since the patients were treated at the clinic and three of the seven patients, or 43 per cent, were alive.

The lesion was classified as stage 3 in six cases. Only one, or 17 per cent, of the six patients is known to be alive. In this case, eleven years have elapsed since the patient was treated at the clinic. There was no evidence of recurrence of the lesion when the last follow-up data were obtained.

As might be expected, in *all* of the four cases in which the lesion was classified as stage 4 the patients died of the disease or of incidental complications.

Grade of Malignancy.—The effect of the grade of malignancy and of the type of lesion will be considered in a subsequent paper on this subject.

Duration of Symptoms.—Although the number of cases in this series is too small to justify definite conclusions, it would appear that better results will be obtained when the lesion is recognized in seven months or less after the onset of symptoms. In the twenty cases in which the patients were followed more than five years, good results were obtained in 38 per cent of cases in which the tumor was recognized within nine months after the onset of symptoms but in only 14 per cent of cases in which the symptoms were of longer duration.

Curiously, however, five patients who had had symptoms for a year or more all lived at least one year after they were treated at the clinic. One lived one year; one, twenty-two months; one, two years; one, six years, and one is still living after ten years. In contrast, a group of ten patients (not including patients classified as "cured") who had had symptoms for less than one year fared less well; one lived fifteen months but the remaining nine died in ten months or less from the time the lesion was discovered. It would appear that if a good result is not obtained the patient who has had symptoms of carcinoma for more than one year before the diagnosis is made will survive longer than one who has had symptoms for a shorter period.

*International classification.

Type of Therapy.—It is difficult to draw definite conclusions as to the type of therapy that produces the best results, since this series of cases is relatively small and the different types of therapy have not been used in comparable cases. The findings, however, justify certain statements. Porro cesarean section has produced poor results for the mother in all cases in which it was employed. In cases in which the lesion was operable, the best results were obtained by total hysterectomy. In four of seven cases in which this operation was performed, the patients have lived ten or more years after the operation. In one of three cases in which vaginal hysterectomy was performed, the patient is living ten years after operation.

It is difficult to state how much the prognosis is improved by subsequent use of irradiation therapy. This type of therapy is not necessarily essential since one patient, who is alive twenty-three years after abdominal hysterectomy, was not given supplementary irradiation. In only two instances was irradiation used as the sole treatment in cases in which the lesion might be classified as operable; in both of these cases the patients died of extension of the lesion. In contrast, in a case in which the lesion was stage 3 and the prognosis apparently hopeless, the response to irradiation was excellent. In this case, the patient is free of recurrence of the lesion ten years after treatment.

Summary

A study of 3,570 cases of carcinoma of the cervix observed at the Mayo Clinic in approximately thirty-two years revealed that pregnancy was present in twenty-six, or 0.7 per cent, of these cases when the carcinoma was found. This figure does not necessarily indicate the true incidence of carcinoma of the cervix coincident with pregnancy as all of the 3,570 patients came to the clinic because of carcinoma of the cervix and not because of pregnancy. In the same period covered by this study, 8,500 pregnant women were observed at the clinic.

The average age of the patients in the twenty-six cases in which carcinoma of the cervix was coincident with pregnancy was 32 years. The youngest patient was twenty-five years of age and the oldest patient was forty-one years of age. The prognosis was no worse in the case of young patients than it was in cases in which the patients were older.

The average number of previous pregnancies was 6 and the average number of children was 4. The number of pregnancies apparently did not affect the prognosis. In cases in which the carcinoma was diagnosed in the later months of pregnancy, the lesion usually was well advanced and the prognosis was poor.

Pregnancy may occur after carcinoma of the cervix has developed. A family history of carcinoma was elicited in seven, or 35 per cent,

of the twenty cases which were observed five or more years prior to 1941. The prognosis in these seven cases was better than the prognosis in the remaining cases.

Bleeding was the initial symptom in twenty-three, or 88.5 per cent, of the cases. In 25 per cent of the cases, the patients did not realize that they were pregnant when the diagnosis was made.

No definite conclusions can be drawn concerning the relative value of irradiation therapy; however, it appears that operation is preferable in cases in which the lesion is operable and that supplementary irradiation increases the percentage of good results. This is in contrast to the relative value of irradiation therapy and hysterectomy in cases of carcinoma of the cervix in which the patients are not pregnant.

We are in general agreement with Strauss concerning treatment of carcinoma of the cervix coincident with pregnancy. If the extent of the lesion permits operation and if the fetus is not yet viable, total hysterectomy is followed by irradiation; if the lesion is operable and the fetus is viable, cesarean section is followed by panhysterectomy and postoperative irradiation.

In cases in which the lesion is nonoperable and the fetus is viable, cesarean section is followed by irradiation; in cases in which the lesion is nonoperable and the fetus is not yet viable, sufficient irradiation is employed to treat the lesion; incidentally, abortion occurs.

In cases in which the lesion is operable, total abdominal hysterectomy has produced the best results. In 57 per cent of the cases in which this procedure was employed, the patients were free of recurrence five years after the operation.

In this series of cases of carcinoma of the cervix coincident with pregnancy, many of which were observed before the present methods of treatment were developed, the prognosis appeared to be at least as favorable as the prognosis of carcinoma of cervix that is not associated with pregnancy. Of the twenty patients who were followed, 30 per cent were free of recurrence five or more years after they had been treated at the clinic.

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PELVIC INFLAMMATORY DISEASE OF SPECIFIC ORIGIN

A Comparative Study of Two Series of Cases From the Charity Hospital of Louisiana at New Orleans, With Special Reference to Recent Therapeutic Improvements and Their Effect on the Mortality

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RECENTLY I found in the files of my brother, the late Dr. C. Jeff Miller, some of the tabulated data used as the basis of the studies which he had published in 1927 and 1928[1, 2] on specific salpingitis and the allied conditions loosely classified as pelvic inflammatory disease. The files also contained the abstracts of material from periodicals and other literature used as background for these studies. Although some detailed data which would have been useful are missing, enough material was found to make me believe that a comparative analysis of the same diseases at this time would be of interest, particularly in respect to the effect upon the mortality of the therapeutic changes introduced in more than fifteen years which have elapsed since the original studies were published. A survey of the gynecologic literature for the past five years has confirmed my impression that only a rather limited number of surveys of pelvic inflammatory disease have recently been published, although to gynecologists who practice in areas where there are large Negro populations only uterine fibroids present problems of equal importance.

C. J. Miller's studies were based on (1) a gross analysis of the 6,184 cases of pelvic inflammatory disease treated in the Charity Hospital of Louisiana at New Orleans during the 10-year period ending January 1, 1926 (Table I), and (2) a detailed analysis of 300 recent consecutive surgical cases from the same institution, and of 300 similar cases from Touro Infirmary in the same city. I have confined my own studies (Table I) to the New Orleans Charity Hospital, where, generally speaking, specific pelvic inflammatory disease is seen in far greater frequency and usually in far graver aspects than at private institutions. They include (1) a gross analysis of 3,072 cases of salpingitis and allied conditions treated over the three-year period ending September 30, 1942; (2) a detailed analysis of the 16 surgical and 14 nonsurgical deaths which occurred during the same period; and (3) a detailed analysis of 500 nonfatal surgical cases treated during the same period, the object of the latter analysis being chiefly a determination of recent trends of treatment.

General Considerations

Of the specific origin of most cases of pelvic inflammatory disease at the New Orleans Charity Hospital, the gynecologists who treat them

have very little doubt. When acute primary infections of the lower genital tract are seen promptly, which they seldom are, even in white women of the class treated at this institution, bacteriologic proof of gonorrheal disease is forthcoming in a large number of cases. When the infection has reached the tubes, bacteriologic proof of a specific origin is usually lacking, partly because laboratory examinations are not performed as often as they should be, and partly because even cultural methods, though superior to smears,[3, 4] are themselves unsatisfactory in most cases. Lewis,[5] for instance, was able to diagnose only six of 80 cases of pelvic inflammatory disease at the New Haven Hospital by cultural methods, and Mahoney's incidence of successful cultures (cited by Lewis) in 1,598 prostitutes was only 21 per cent, which approximates the percentage of success in the cases at Charity Hospital in which cultures were made. Be this as it may, the disease is overwhelmingly more frequent in Negro women (Table II), and, as C. J. Miller pointed out, when pelvic pathology in women of this race at this institution is interpreted in the light of the findings in the Negro male population, it can obviously be attributed to specific infection in all but a small proportion of cases.

The history of pelvic inflammatory disease is usually typical, particularly in young women, but in women of the social level treated at Charity Hospital, either because of the patients' ignorance or because

TABLE I. TWO SERIES OF CASES OF PELVIC INFLAMMATORY DISEASE AT CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

	C. J. MILLER* 1927	H. E. MILLER 1943
Total cases	6,184	3,072
Deaths	153	30
Per cent	2.5	1.0
Surgical cases		2,128
Deaths		16
Per cent		0.75
Nonsurgical cases		944
Deaths		14
Per cent		1.87

*The breakdown for this series into surgical and nonsurgical cases is not available. The mortality is a case mortality. In the period covered by the figures the unit system of admission was not in effect, and readmissions were counted as if they were new cases. The actual patient mortality would therefore be higher than 2.5 per cent, and the difference between this mortality and the less than 1 per cent patient mortality reported for the recent period is actually greater than is apparent.

TABLE II. COMPARATIVE WHITE AND NEGRO STATISTICS OF PELVIC INFLAMMATORY DISEASE IN A RECENT THREE-YEAR PERIOD AT CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

	CASES	DEATHS	PER CENT
Total cases	3,072	30	0.1
White	733	6	0.82
Negro	2,339	24	0.1
Surgical	2,128	16	0.75
White	432	3	0.69
Negro	1,696	13	0.77
Nonsurgical	944	14	1.87
White	301	3	1.0
Negro	643	11	1.7

of their deliberate intent to deceive, their stories are frequently confusing. Thus in the 500 cases recently studied in detail, although 25 women classified themselves as single, eight of them were later found to have had abortions or full-term pregnancies or both, and pelvic examination in the remaining cases vitiated the professions of virginity. In addition, many of the 475 women who classified themselves as married admitted promiscuous sex relations.

A definite history of recurrent attacks of pelvic disease, which occasionally were frankly stated to be due to "pus tubes," was obtained in 64 cases, and 33 other patients had been repeatedly treated in the hospital during recurrent acute attacks or had been discharged to cool at home in preparation for operation. Unilateral salpingectomy had been previously performed in 28 other cases, colpotomy (in one instance on two occasions) in three cases, and abdominal drainage and drainage of a Bartholin gland abscess in one case each. Laboratory examination of the excised tubes revealed salpingitis isthmica nodosa in 63 cases, and more careful examination would probably have materially increased the percentage. Schenken and Burns[6] have recently studied this condition at the New Orleans Charity Hospital and have again called attention to the association between it and gonorrheal infection.

In the 500 cases recently studied at Charity Hospital exact data as to the onset of the original infection could be secured in less than 10 per cent, and the apparent time of extension to the tubes could be secured in only 31 instances. The upward extension was precipitated by abortion (in several instances criminal and in one repeatedly criminal) in nine cases, by delivery in 11, by the sex act in five, and by a menstrual period or by operation on the cervix in three each. In one of the fatal cases the tubal disease clearly dated from conization of the cervix.

It is hard to explain, although the fact is well known, why some women with almost completely frozen pelves are in relatively good health, while others, with far less demonstrable pathology, are for all practical purposes complete invalids. Negro women, who as a group present far more serious pelvic changes than white women, are inclined to be much less affected by them and frequently ignore their illness until pain becomes severe or until they are incapacitated by other symptoms. These differences in reaction can perhaps be attributed to racial differences in the threshold of pain. Whatever the reason, they are of great practical importance: In the group of fatal cases one Negro woman remained at home without treatment until she was actually moribund, while three others died so soon after admission to the hospital as to make all treatment futile. Incidentally, the tendency to take purgatives for abdominal pain was, as usual, evident in both Negro and white women.

Since a vaginal discharge is a prominent feature of pelvic inflammatory disease, it is surprising to find it complained of by only 38.6 per

cent of the 500 patients, which is about the same proportion reported in Miller's earlier series. These low percentages are corroborated by Guerriero and Arnell,[7] who found that less than a third of 433 pregnant women with nonbloody vaginal discharges studied at the New Orleans Charity Hospital considered this symptom worth mentioning in their histories, or actually denied its existence, although, as in these two series, a vaginal discharge was actually and profusely present in a much larger number on pelvic examination.

Although diagnosis was not difficult in most of the 500 cases emergency operations were performed on the mistaken diagnosis of acute appendicitis in eight instances. Boyce[8] has recently reported 60 other "unnecessary" emergencies of the same kind, and I am completely in accord with his conclusion that such operations are usually justified. In contrast to the absence of mortality in these 60 cases, he cites, from other studies of his own, three deaths in 46 cases of acute appendicitis in which operation was postponed for varying intervals on a mistaken diagnosis of pelvic disease, as well as seven deaths from acute appendicitis in which operation was not performed at all on the same mistaken diagnosis. I am also in agreement with Boyce's warning that if the abdomen should be opened on an apparently mistaken diagnosis and pelvic inflammatory disease should be found, the surgeon should usually refrain from pelvic surgery, though, regardless of the state of the pelvis, he should search for and thoroughly examine the appendix, to be certain that it is not also the site of a primary pathologic process.

Nonsurgical and Adjunct Therapy

Results at the New Orleans Charity Hospital support Lewis'[9] discouraging statement that all forms of therapy in pelvic disease have to date been remarkably unsuccessful and amount to little more than watchful waiting, with surgical interference when necessary. They also support his statement that in the past, therapeutic methods have been credited with curing patients who really cured themselves and who frequently recovered in spite of rather than because of the treatment they had received. For my own part, I do not exclude chemotherapy when I say that except for general measures, which must frequently be followed by surgery, no treatment of specific pelvic inflammatory disease has to date given even approximately satisfactory results. I would go even further and say that the general measures usually employed with most other forms of therapy are probably more responsible than any special measures which may be employed for such results as are achieved.

Diathermy (15 cases), [the Elliott treatment (seven cases) and protein therapy (five cases)] were used in the recent series studied at Charity Hospital, with no notable and no permanent results from the standpoint of either clinical or anatomic improvement. My results in private practice with all three methods have been equally poor. G. A.

Williams,[10] whose statistics, because they relate to Negroes, are peculiarly comparable to my own, states that a prolonged trial of protein therapy at Grady Hospital in Atlanta has indicated its uselessness in this race. He also sets forth the shortcomings of the Elliott treatment in a public institution. Very significant is the fact that of 369 women treated by this method at Grady Hospital, approximately 40 per cent either disappeared from observation or failed to cooperate long enough to permit adequate treatment. Of those observed from four to 26 months—the former period being much too brief to warrant statements as to end results—1.9 per cent died, 15.8 per cent showed no improvement, and only 28.7 per cent could be regarded as cured. These results, Williams points out, are by no means as favorable as those reported by other authors in white or white and colored patients combined. As might have been expected, the best results were obtained in recent acute cases and the least good in chronic cases with frozen pelves.

Chemotherapy.—The statement that I do not regard the greatly improved mortality of pelvic disease at the New Orleans Charity Hospital in recent years (Table I) as due to chemotherapy will occasion no surprise to those who have used the sulfonamides in this condition. Goff's[11] statement that the results of chemotherapy in female gonorrheal infections are proving more and more disappointing has found many echoes in addition to my own. Barrows and Labate,[12] for instance, whose studies were made with smears and not with cultural methods, found that primary attacks of less than five days' duration were apparently cured after a week of chemotherapy in 70 per cent of mild and 66 per cent of moderate cases, but that cases of longer duration, whether mild or severe, and recurrent cases showed no adequate response. J. T. Williams,[13] after reviewing the literature, which does not contain a great deal on chemotherapy in salpingitis, concluded that the results are not likely to be good after the initial attack or after pelvic masses have formed; most cases at Charity Hospital fall into these two groups. In a treated series of cases, contrasted with a control series similarly managed except for the omission of chemotherapy, Williams found no special differences in regard to improvement of symptoms, duration of fever, and other clinical phenomena, while the incidence of surgery was substantially the same in both.

An evaluation of chemotherapy in the Charity Hospital series presents certain difficulties. In many cases it was not indicated. In many instances it was impossible to determine whether the drugs were used tentatively (a policy which Stokes[14] has warned against on the ground that it may establish a presumption of malpractice) or as a deliberate phase of the adjunct treatment. All routes of administration were used, as were most of the suggested dosages, and neoprontosil, sulfanilamide, sulfapyridine and sulfathiazole were all employed, sometimes in the same case.

Chemotherapy does not seem to have been employed in any instances in the primary infection of the lower pelvis, chiefly because not more than two or three patients, at the most, seem to have received treatment at that time. Only 20 patients, in all of whom the results were poor, stated that they had taken sulfonamides in some form before their admission to the hospital with pelvic inflammatory disease. I have no doubt, judging by my own experience in private practice, that many other patients were thus treated and merely did not know what drugs they were receiving, but it was naturally impossible to identify this group.

Chemotherapy was used either in an endeavor to avoid surgery or as a preoperative measure to control infection in 21 of the 238 patients who entered the hospital with some degree of fever. All of the cases were of long standing and in all the results were poor, as might have been expected. Experience has shown that chemotherapy does not give good results in encapsulated appendiceal abscess, and there is no reason to anticipate better results when chemotherapy is practiced after an inflammatory reaction has resulted in closure of the tubes, accumulation of exudates, development of tuboovarian abscesses, and extensive structural alterations. These changes, as already pointed out, are seen in a large majority of cases of pelvic disease at Charity Hospital, particularly in Negro women, most of whom present recurrent disease, and it is unreasonable to expect chemotherapy or any other form of nonsurgical treatment to effect the miracle of an anatomic cure. Furthermore, if Barrows and Labate's[12] criterion be used, that the patient must be treated within five days of her primary attack, good results could not have been expected in most cases in this series, since only 30 of the 500 women were seen within the first week of their illness.

Although I have no statistics on this point, I think it well to emphasize, in view of the carelessness with which the sulfa drugs are sometimes used, that early assumption of cure, unconfirmed by cultural methods, is both misleading and dangerous. This is particularly true of Negro women, whose mode of living frequently violates all the laws of sex hygiene. Lewis[9] endeavors to meet this risk by issuing prescriptions for only 48 hours at a time, but the defect of this precaution, which requires attendance at the clinic every third day, is that it breaks the continuity of bed rest, which personally I regard as the most important phase of treatment.

According to the records, sulfanilamide was used in the peritoneal cavity and in the layers of the wound in 35 of the 469 cases in which laparotomy was performed. Again I suspect that the number was much larger and that the operators merely failed to make their operative notes complete. An estimation of the exact results is impossible, but it is fair to say, on the basis of my own experience, that many potential infections are averted by this method and that many actual

infections are controlled and rendered less virulent. It may be significant, furthermore, that this method was not used in any of the 16 fatal surgical cases, in seven of which peritonitis was the cause of death and in one of which a massive wound infection played an important part in the fatal outcome.

Chemotherapy, chiefly by the oral route, was used as a postoperative measure in 99 cases. In 37 the indication was urinary tract infection, usually limited to the bladder, and the results in all cases were prompt and good. In some 10 cases the indication for chemotherapy was not clear and the method seems to have been used only tentatively. In the remaining cases peritonitis was either present at operation or its development seemed likely. Though improvement eventually occurred in all of these cases, it was considerably less prompt than when urinary tract infection was the indication for chemotherapy, and other measures, such as infusion, transfusion, and intestinal decompression, should probably be credited with a large part of the final good results. In a few instances long continued pyrexia terminated within a day or two after withdrawal of the sulfonamide, and was clearly a reaction to the drug.

The sulfonamides, chiefly in the form of sulfathiazole, were used in every one of the 14 fatal nonsurgical cases, in several of which, however, death occurred too promptly for any form of therapy to be effective. They were used both before and after operation in all the fatal cases (11) in which infection was responsible for the fatality. They do not seem to have affected the outcome even transiently in any case in either of these groups, and in one or two of the nonsurgical cases they apparently led to the complacent belief that other measures might safely be omitted; at any rate, such measures were instituted late. Two instances of dermatitis and three of jaundice in the fatal cases and one instance of jaundice in a nonfatal case are evidence that this is not a harmless form of therapy, especially in patients whose initial general condition is poor.

General Measures.—I have examined with interest the methods of nonsurgical and adjunct therapy employed in C. J. Miller's[1, 2] reported cases and advocated in the material from the literature which he used as background. They consisted chiefly of complete bed rest, sometimes in the Fowler position; the local application of icecaps or heat; a liquid or semiliquid diet; measures for the control of pyrexia; regulation of the bowel function (although some writers advised the daily use of a saline purgative, Miller considered anything more forceful than a low enema to be unnecessary if not harmful); and hot or cold douches for the control of annoying discharges. Miller considered the local application of iodine or other antiseptics to be futile if not dangerous, and he warned that pelvic examinations should be performed very gently and only as necessary to follow the progress of the disease.

General measures which put the pelvic structures at absolute rest are still the basis of all successful nonsurgical treatment of pelvic inflammatory disease, but the adjunct treatment of the condition is now very different. Very striking in Miller's reported cases and in the current literature which he abstracted is the absence of emphasis on fluid therapy and blood transfusion. In his reported cases fluids were administered parenterally only to the occasional patient and usually by proctoclysis and hypodermoclysis. Transfusion seems to have been chiefly an ante-mortem measure. In some papers which he abstracted fluid therapy is not even mentioned, and transfusion is suggested only by Doherty,[15] an advocate of immediate radical operation for acute salpingitis, who proposed it only for "septic cases."

In the period between 1927 and 1943, there have been important changes in the concept of the fluid balance of the body, infusion has become a part of the surgical routine, and massive transfusion has been developed. A comparative analysis of the recent and the original series of cases leaves no doubt that it is the careful application of these advances, plus more adequate preoperative and postoperative care, especially with respect to replacement of body fluids and maintenance of the fluid balance, which accounts for the chief reduction in the mortality of specific inflammatory disease in recent years at the New Orleans Charity Hospital.

In the recent series even moderately dehydrated patients were infused one or more times before operation if the fluid balance could not be satisfactorily maintained by oral intake, and more than 25 per cent (131) were infused after operation. The more seriously ill patients were thus treated for periods of time which sometimes exceeded 21 days. Forty-one patients were transfused one or more times before operation and 42 were transfused after operation. Infusions and transfusions were also used freely in the fatal cases. One patient in the latter group had 3,600 c.c. of blood before operation, and only two patients were not transfused at all. In one instance the omission seems to have been due to poor judgment. In the other, no donors could be secured, a difficulty which the recent establishment of a blood and plasma bank at Charity Hospital should obviate for the future.

Other adjunct measures, most of them of recent development, were also profitably employed both before and after operation in the recent series. Anemia not serious enough to require transfusion was combated by liver extract and preparations of iron. Suspected or proved vitamin deficiencies were corrected by appropriate measures, as was hypoproteinemia. The rectal tube and prostigmine and similar preparations were used before and after operation as indicated, and constant intestinal decompression was instituted if these simpler measures were not immediately successful. Changes of position and inhalations of carbon dioxide and of oxygen were used as prophylaxis against the development of pulmonary complications.

Postoperative Complications

As a result of these measures, although the first few days after operation were critical in perhaps 40 of the 500 surgical cases, and although 16 patients had prolonged and stormy convalescences, postoperative complications were neither frequent nor serious, except for wound infection. This complication developed in 49 cases, in 12 of which incision and drainage were necessary. Delayed healing was observed in three cases, in one of which a frank hernia developed, but evisceration did not occur in any instance in the nonfatal cases. For the almost 10 per cent incidence of wound infection I have no explanation.

Ileus was rarely observed, and peritonitis developed after operation in only one case in which it had not been present before operation. Postoperative urinary tract infections were serious in only 11 of the 37 cases in which they developed, and pneumonitis and other respiratory tract infections occurred in only 10 cases. Hemorrhage and thrombophlebitis occurred in two cases each, and jaundice and hepatomegaly were observed in one case each, in both instances following chemotherapy.

The incidence of complications in the recent series is several times smaller and the complications were generally much less serious than in C. J. Miller's group. The difference, I am sure, can be attributed to improved preoperative and postoperative therapy. It was definitely not due to the better condition of the patients, for many in the recent series presented serious complications, aside from their pelvic disease. One hundred twelve had hypertensive or cardiac disease, usually improved, incidentally, by bed rest and medical measures instituted before operation. Forty-five had been treated for syphilis, usually incompletely because of their own lapses, and the blood serologic test was presently positive in 119 cases; one patient had tabes dorsalis. Seventeen patients presented hepatomegaly, though tests of liver function were unfortunately not carried out in any case. Six had pyelitis and three nephritis, and some degree of cystitis was initially present in more than a third of the 500 patients; usually these infections responded promptly to simple measures, but when they did not, chemotherapy was employed. Other associated conditions included umbilical hernia (15 cases), ventral hernia (three cases), and diastasis recti (eight cases), lymphogranuloma inguinale (two cases), and pellagra, typhoid fever, and epilepsy (one case each). Sixty-seven patients were obese, many weighing 200 pounds and more. Four were cachectic and three others greatly dehydrated from vomiting and diarrhea. In 103 cases the hemoglobin on admission to the hospital ranged downward from 70 to 28 per cent, and in 62 cases the red blood cell count ranged downward from 3,500,000 to 1,500,000 per cu. mm. Forty-one patients were admitted so gravely ill that long preparation for operation was necessary.

C. J. Miller called special attention to the fact that in the 600 cases he reported, 72 per cent of the postoperative complications, 72 per cent of the postoperative temperature elevations over 101° F., and 16 of the 18 deaths occurred in the patients who had not been properly cooled before operation according to Simpson's[16] criteria. In the 500 cases now reported, 34.4 per cent (172) were also operated on without full adherence to these criteria, this group including, however, the cases in which the ovary was implicated and in which temperature elevations frequently continue until surgery is carried out. On the whole, although the violations of Simpson's criteria were far less marked than in the earlier series, the results of the violations were much the same. Eighty-one per cent (189) of the postoperative temperature elevations over 101° F., and 70 per cent of complications occurred in this group. Of the 75 patients kept in the hospital longer than 10 days (the present desired maximum under crowded conditions and necessary economy), 54 per cent had been incompletely cooled, and 44 per cent of the patients discharged with some degree of fever had also been incompletely cooled. In the fatal surgical cases, however, the patients were in such condition in only three or four cases, at most, as to make the outcome anything but doubtful, regardless of how long they had been cooled.

Rupture of Pelvic Masses.—Until I had completed this study I should have subscribed to the general idea that rupture of pelvic masses is an unlikely accident in pelvic inflammatory disease. I have necessarily changed my mind. Of the 41 tuboovarian masses included in the 500 nonfatal surgical cases, two had ruptured before operation and the same accident had occurred in three of the 16 fatal surgical cases. There were also three instances of rupture, all proved by autopsy, in the 14 fatal nonsurgical cases. In one instance, the accident followed so closely upon bimanual examination as to suggest a possible cause and effect relationship. I have already located nine other instances, seven of them proved by autopsy, of this supposedly infrequent accident in a study I am now making of gynecologic deaths at the New Orleans Charity Hospital over a recent period. The tabulated data I have available from C. J. Miller's study do not permit a determination of how many of the five instances of rupture in his 600 cases terminated fatally.

Surgical Therapy

A few comments are necessary on the various surgical procedures carried out in this series (Table III). In two of the six cases in which surgery was limited to simple drainage of the abdominal cavity, colpotomy had previously been carried out. The eight cases in which only appendectomy was performed have already been discussed. In the three cases in which only exploration was performed it was the surgeon's opinion that any attempt to remove the infected pelvic struc-

tures would be attended with too much risk because of the involvement of the intestines in the pelvic adhesions. In such cases the corneal resection devised by Falk[17] might be of value, though I have had no personal experience with it. The basis of the operation is the pathologic fact that recurrent salpingitis is caused by repeated upward extension of infection along the endometrium, and its rationale is the interruption of this epithelial continuity. Falk's excellent results from the Harlem Hospital, where the material is rather similar to that of the New Orleans Charity Hospital, include 78 per cent of anatomic, 85.5 per cent of clinical, and 97.8 per cent of economic cures, the latter being a consideration of extreme importance in women of these social levels.

TABLE III. COMPARATIVE SURGICAL PROCEDURES IN TWO SERIES OF CASES OF PELVIC INFLAMMATORY DISEASE AT CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

	C. J. MILLER* 1927	H. E. MILLER 1943
Total cases	600	500
Bilateral salpingectomy	436	425
with hysterectomy		391
with bilateral oophorectomy		364
with unilateral oophorectomy		24
Unilateral salpingectomy	154	34
with hysterectomy		31
with oophorectomy		10
Drainage only	3	6
Plastic on tubes	17	3
Exploration only		3
Exploration and appendectomy		8
Colpotomy		21
†Appendectomy also	343	273
†Drainage also	78	10

*All the details of the operations in this series are not available, but it is known that hysterectomy was done in 99 cases.

†These figures are overlapping.

Specific pelvic disease is one of the few conditions in gynecologic practice in which conservative surgery is frequently ill advised. The tendency in this disease is for unilateral infection to become bilateral, and the chances of functional recovery of affected tubes are notably poor. In the 500 cases I am reporting, 21 patients, 4.2 per cent, had already been submitted to previous conservative surgery (exclusive of the group in whom only exploration or only colpotomy had been carried out), as had 3 per cent of the patients in C. J. Miller's series. The proportion of previous conservative surgery was 6.3 per cent in 94 cases reported by Craig and Kraff,[18] and it was 24 per cent in Whitehouse's[19] series.

In C. J. Miller's series the incidence of bilateral salpingectomy (Table III) was 72.6 per cent; in my own series it had risen to 80.5 per cent. I seriously question the wisdom of, or the justification for, the plastic operations on the tube, in one instance combined with resection of the ovary, done on three Negro women in my own series, but the figure is an improvement over the earlier series, in which resection of, or

plastic operations on the tube were done in 17 instances and resection of the ovary or ovarian grafting was done in 34 cases. In twenty-five years' experience at the New Orleans Charity Hospital I have never personally seen a case in which I regarded plastic surgery on the tubes as justified.

The difference in the incidence of hysterectomy in my own and in the earlier series is striking (Table III), 80 per cent (401 cases) versus 16.5 per cent (99 cases). The tendency toward more radical surgery is entirely justified. When the tubes have been removed the uterus is always a useless and frequently a troublesome organ. This is a serious consideration in women whose livelihood depends upon their own efforts, quite aside from the risk of a second operation. That this risk is real is shown by McDermott's[20] figures: In a series of 839 hysterectomies, 11 per cent of the patients had previously been submitted to unilateral or bilateral salpingectomy.

Since the tendency at the New Orleans Charity Hospital is more and more to perform total hysterectomy in the absence of indications to the contrary, the fact that approximately 37 per cent (147) of the 391 hysterectomies were supravaginal may be interpreted as indicative of the serious condition of many of these patients. Of the 10 hysterectomies performed in the 16 fatal surgical cases, however, only three were supravaginal, and in view of the generally poor status of these patients it might have been the part of wisdom to use the incomplete procedure more often. When performed with due regard to contraindications, the complete operation, in spite of an impression to the contrary, does not increase the mortality, and sometimes is attended with fewer deaths. In my own study with Prejean[21] from the New Orleans Charity Hospital the mortality for complete hysterectomy was 1.33 per cent, against 2.75 per cent for the supravaginal operation. An additional advantage of the complete operation is the absolute protection it furnishes against the later development of cervical malignancy. In one of the cases in the present series the patient returned in four months with carcinoma of the cervix so far advanced that it evidently had been present when the supravaginal hysterectomy was done as part of the operation for pelvic disease. I might add that Prejean and I found carcinoma of the cervix as an entirely unexpected finding in 12 of the 255 complete hysterectomies which we reported in 1941.

Appendectomy had previously been performed in 30 of the 500 cases, and was carried out at operation in 273 of the remaining 449 laparotomies (63 per cent), as compared with an incidence, so far as I can calculate from the data available, of about 56 per cent in the earlier series. It is generally routine in gynecologic surgery at the New Orleans Charity Hospital when it does not add materially to the risk or prolong the operation unduly. Under the most favorable circumstances, however, it carries a small additional risk, and the fact that

it was not done in so many possible cases can be construed as evidence of surgical prudence. Appendectomy was performed in three of the fatal surgical cases, and in one, at least, seems to have been an error of judgment. Medical consultants had warned that the patient was an extremely poor risk because of her cardiac state.

The approximately 2 per cent incidence of drainage in the series I am reporting (10 of 473 possible cases) is to be compared with the 13 per cent incidence reported by C. J. Miller (78 of 597 cases). The indications in the second series were chiefly oozing and uncertainty as to hemostasis. Even when tuboovarian abscesses were ruptured in the course of removal, as happened in 19 instances, it was seldom employed. The present plan of drainage only on strict indications has played a definite part, I am sure, in the improved mortality of surgical pelvic inflammatory disease at the New Orleans Charity Hospital, and I am equally sure that it has reduced the number of postoperative abdominal complications.

As in all similar institutions, the surgery at Charity Hospital continues to be done, as it has always been done, by surgeons of all grades of training and experience. Since C. J. Miller's report was made, however, a resident system has been instituted, and a large proportion of the surgery in the period covered by my report was done by these young men. The lowered mortality is a credit to them and to their training, and the great improvement in preoperative and postoperative care must in all fairness be attributed to their conscientious work.

Pelvic Inflammatory Disease in Negro Women

It is unrealistic to discuss gynecologic statistics from the New Orleans Charity Hospital without calling attention to the high incidence of certain diseases, especially pelvic inflammatory disease and uterine fibroids, in this race. More than 76 per cent of the total incidence of specific pelvic disease over the three-year period covered by this report (Table II) occurred in Negro women, as did more than 79 per cent of the surgical salpingitis, and 80 per cent of the total mortality. In evaluating these proportions, the hospital ratio of admissions, which averages 55 white to 45 Negro patients, year in and year out, should be borne in mind.

In the 500 cases studied in detail, 305 of the 430 Negro women presented uterine fibroids, usually very large, as compared to 12 of 70 white women, in whom the growths were uniformly small. This association is well known to surgeons who operate on Negro women. Torpin and his associates,[22] for instance, found a 54 per cent incidence of pelvic inflammatory disease in Negro women operated on for fibroids, and a 40 per cent incidence of fibroids in Negro women operated on for pelvic inflammatory disease.

Everything that Miller wrote sixteen years ago about the treatment of pelvic inflammatory disease in Negro women still holds true. She

is difficult to separate from her infected partner, and she seldom cooperates fully in attempts at prolonged physical and sexual rest. Whether the cooling period is spent in the hospital or at home, there are frequent defections, and even when the prescription is obeyed, the disease tends toward chronicity and frequent exacerbations. Recovery under nonsurgical therapy is not the rule. Surgical procedures are necessary in a large proportion of all cases and are frequently very difficult. Pathologic changes include tuboovarian abscess, pyosalpinx, and cul-de-sac abscesses, and the pelvic viscera may be so glued together that their identification, let alone their separation, sometimes seems impossible, as indeed it was so regarded in at least three cases in my own series. When all the facts are taken into consideration, the mortality is low enough to warrant the postulate that Negro women either have a higher degree of resistance to infection than white women, or that they develop some special immunity to the gonococcus. It should be added that the hygiene of the Negro home is frequently bad, and that the woman with a gonorrheal infection is likely to infect other members of her family while her disease is proceeding on its upward course.

Summary and Conclusions

1. A study of specific pelvic inflammatory disease at Charity Hospital of Louisiana at New Orleans shows that the over-all mortality in a series of 6,184 cases reported in 1927 and 1928 was 2.5 per cent, as compared with a mortality of slightly less than 1 per cent in 3,072 cases treated at the same institution over a recent approximately three-year period and reported herewith.

2. Pelvic inflammatory disease in Negro women is more frequent than in white women, is much more frequently associated with fibroids, and as a result of neglect is often much more serious.

3. Rupture of tuboovarian masses, although generally believed to be unusual, was observed in eight cases in this study, in six of which it was fatal.

4. Acute appendicitis furnishes the chief difficulty in differential diagnosis, and statistics show that exploration is justified if the confusion cannot be cleared up promptly. Bacteriologic diagnosis, whether by smear or culture, is highly unsatisfactory.

5. Except for general measures, no treatment of pelvic disease gives even approximately satisfactory results. Chemotherapy is disappointing in infections above the external cervical os, but is a useful adjunct measure in properly selected cases, though it is by no means free from risk.

6. Surgery is ultimately necessary in a large proportion of cases of recurrent salpingitis, particularly in public institutions with a large number of Negro patients. Conservative surgery must frequently be followed by secondary surgery, and plastic operations on the tubes

have little to commend them, especially in women of the poorer classes. Drainage should be used with discretion, and appendectomy should be omitted in poor risk cases and in those in which operation has been unduly prolonged.

7. An analysis of 500 recent surgical cases at Charity Hospital, compared with an analysis of 600 surgical cases from this institution and from Touro Infirmary reported in 1927 and 1928, shows that the recent improvement in the mortality of pelvic inflammatory disease can be attributed to: the free use of fluids before and after operation, especially the parenteral administration of fluids; the free use of transfusion; the institution of measures to correct mild degrees of anemia and vitamin and protein deficiencies; the prevention of ileus by the prompt use of intestinal decompression and other measures; the prevention of pulmonary complications by various prophylactic measures; the employment of drainage only on strict indications; the performance of supravaginal rather than complete hysterectomy in poor risk cases; the omission of appendectomy in all but good risk cases. Chemotherapy played only a minor part in the improved results and was not curative in any case, but was effective as an adjunct form of treatment in properly selected cases. The basic reason for the improvement in the preoperative and postoperative care, which in turn was the basis of the improvement in the mortality, was the institution of a resident system in the hospital.

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Medical Arts Building

IODINE VAPOR TECHNIQUE VERSUS CARBOLFUCHSIN STAIN FOR VAGINAL SMEARS

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THE iodine vapor staining of vaginal smears, as described by Mack,[1-4] has proved to be a quick and simple quantitative test for cellular glycogen. From older and more difficult techniques it has appeared that the glycogen content of the vaginal mucosa cells is an indication, at least in a general way, of bodily ovarian or estrogenic hormone activity. As a consequence, the newer method, being easy and rapid, may be found after further study to have considerable practical application. As one test of its accuracy in reflecting ovarian hormone activity, a comparison was made of daily vaginal smears stained by iodine vapor with duplicates prepared by one of the older methods which show variations in grading according to cellular size and type.

The iodine vapor technique used has been described before[1-4] and is briefly as follows:

1. *Preparation of Smears.*—A cotton applicator is inserted into the vagina and twirled lightly (one complete rotation) against the vaginal wall. The cotton end of the applicator is then rolled lengthwise over the surface of a clean glass slide. By rolling, rather than rubbing, a uniformly thin film of cells, with minimal clumping and cell distortion, results. The film dries almost immediately and may be stained at once.

2. *Staining of Smears.*—Staining is accomplished simply by laying the slide, face down, over a shallow dish containing Lugol's solution. Iodine vapors which arise insensibly from the solution suffice to stain the glycogen-containing cells in two or three minutes. Microscopic examination may be carried out immediately. Although stains made in this manner fade in twenty-four to forty-eight hours, restaining by the same method may be carried out repeatedly if subsequent examinations are desired.

Following is the system of grading, based on the glycogen and its intracellular distribution:

Grade I.—Complete glycopenia. Smears of this type contain only small yellow cells of varying sizes and shapes and large amounts of amorphous cellular debris. In extreme degrees there is marked paucity of epithelial elements.

Grade II.—This grade is marked by a greater abundance of epithelial elements than Grade I. Iodine vapor staining depicts glycogen in irregular brown deposits at the cell margins or scattered irregularly throughout the cytoplasm (''mottled cells''). Diffusely stained brown cells, usually of the small round variety (''deep cells'') may also be present in small numbers. Many glycopenic yellow cells are also present.

Grade III.—A further increase in cell numbers is evident in this grade as compared to the preceding. The cells are larger and more regular. The diffusely stained cytoplasm has a light brown color. Noniodophilic yellow cells are also present in abundance.

Grade IV.—This grade is easily recognized by the presence, almost exclusively, of large, flat, deeply stained brown iodophilic cells, singly or in large clumps. This grade represents maximal estrogenic effect and corresponds to the smear of the normal proliferative or follicular phase.

The duplicate smears were stained by a slight modification of Geist and Salmon's technique,[5] the chief differences being that, (1) the smears were made from applicators as described for the iodine method, and (2) staining was done with ordinary carbolfuchsin. These changes are rather unimportant but did save a little time since the quickly prepared smears dried almost immediately, and the staining was practically instantaneous.

The Geist and Salmon technique, though requiring considerably more skill in microscopy than the iodine vapor stain, is, however, much simpler than the other rather impractically complicated older methods. It fails to demonstrate minor variations such as differences in cornification which are shown by some stains, but in general is quite adequate for satisfactory classification of the smears into four groups according to estrogenic deficiency or sufficiency, as follows:

Reaction I.—Marked estrogenic deficiency. Complete or nearly complete absence of large epithelial cells. Presence of variable numbers of small, deep or basal cells with large nuclei. Often abundant red and white blood cells.

Reaction II—Moderate estrogenic deficiency. Still a considerable number of deep cells but also a varying number of large epithelial cells. Fewer blood cells.

Reaction III.—Slight estrogenic deficiency. Predominance of large epithelial cells. Only occasional deep cells and blood cells.

Reaction IV.—Estrogenic sufficiency. Numerous large, clearly outlined, squamous cells with small nuclei. No basal cells or blood cells.

Material

The vaginal smears for this study were obtained each day from 21 definitely postmenopausal women with varying degrees of estrogenic deficiency as indicated by both vaginal epithelial atrophy and cellular glycopenia. Three of these women received desiccated thyroid gland in one grain doses for 7 days, while the other eighteen were divided into six groups of three each to whom were given different estrogenic substances or combinations of such. The eighteen subjects who received estrogenic substances were the same as those whose iodine vapor smear findings were illustrated by Figs. 6 to 11 in the last report by Mack.[4]

TABLE I. DESICCATED THYROID GLAND—ONE GRAIN DAILY FOR SEVEN DAYS

PATIENT	STAIN	THYROID GLAND												
17	Iodine vapor	1	2	2	2	2	2	2	2	2	2			
	Fuchsin	1	2	2	2	2	2	2	3	2	2	2	2	2
19	Iodine vapor	2	1	2	2	2	2	2	2	2	2			
	Fuchsin	1	2	2	2	2	2	2	2	2	2	1	2	2
20	Iodine vapor	2	1	1	1	1	1	2	1	1	1			
	Fuchsin	1	1	1	1	1	1	1	1	2	1	2	1	1

Comparisons of the daily duplicate smears stained by the two methods are shown in the accompanying Tables. The digits correspond, of course, to the "grades" and "reactions" described above. Omissions indicate missing smears for the days indicated.

TABLE II. CRYSTALLINE ESTRONE—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	ESTRONE	
5	Iodine vapor	2 2 2 2 2 3 4 4 4 4	4 3 3 3 2 2 2 3 2 2 2
	Fuchsin	2 2 3 3 3 4 4 4 4 4	4 3 4 4 4 4 4
27	Iodine vapor	2 2 3 3 3 4 4 4 4 4	4 4 4 4 4 4 3 3 3 3 3
	Fuchsin	2 2 3 3 4 4 4 4 4 3	3 4 4 4 3 3 3
7	Iodine vapor	1 1 1 2 2 2 2 2 3 2	2 2 2 2 2 2 1 1 1 1 1
	Fuchsin	1 1 1 2 2 2 3 3 3	2 2 2 2 3 3 3

TABLE III. ESTRIOL—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	ESTRIOL	
12	Iodine vapor	1 2 2 2 1 1 3 3 3 2	3 3 3 2 2 2 2 3 2 2 2 2
	Fuchsin	2 2 2 2 2 2 2 2 2 2	2 2 2 2 2 2 2 2
13	Iodine vapor	3 3 3 3 4 4 4 4 4 4	4 4 3 3 3 3 3 3 3 3 3 3
	Fuchsin	2 2 2 2 3 3 4 4 4	4 4 4 4 4 3 3 3 3
14	Iodine vapor	2 2 2 1 1 2 2 2 3 3	3 3 3 2 1 2 1 2 2 2 2 2
	Fuchsin	2 2 2 3 3 3 3 4 4	4 3 3 2 2 2 2 2

TABLE IV. ESTRONE, ESTRIOL MIXTURE—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	ESTRONE, ESTRIOL	
2	Iodine vapor	2 2 2 2 2 2 3 3 3 4	4 3 3 2 3 2 2 2 2 2 2
	Fuchsin	2 2 2 2 2 2 2 2 2 3	3 3 3 3 3 3 3 3 3
3	Iodine vapor	3 2 2 2 3 2 3 3 4 4	4 4 4 2 3 2 3 2 2 2 3 2 2
	Fuchsin	2 2 2 3 3 4 4 4 4 4	4 4 3 2 3 4 3 4
4	Iodine vapor	2 2 2 2 2 2 4 4 4 4	4 4 4 4 4 4 3 2 2 3 3 2
	Fuchsin	2 2 2 2 2 3 3 4 4	4 4 4 3 4 3 3 3

TABLE V. ALPHA ESTRADIOL—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	ALPHA ESTRADIOL	
23	Iodine vapor	2 2 2 2 2 2 3 3 3 4	4 3 2 2
	Fuchsin	1 1 2 2 2 2 3 4	
28	Iodine vapor	1 2 1 1 2 2 2 2 3 4	4 4 4 4
	Fuchsin	1 2 2 2 2 3 3 4	
30	Iodine vapor	1 1 1 2 2 3 3 3 3 3	3 3 4 4
	Fuchsin	2 3 3 3 3 3 3 3	

TABLE VI. DIETHYLSTILBESTROL—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	STILBESTROL	
8	Iodine vapor	2 2 3 3 3 3 3 3 4 4	3 3 3 3 2 2 2 2 4 2 1 1
	Fuchsin	3 3 3 3 3 4 4 4 4	4 4 4 4 3 3 2 2
10	Iodine vapor	2 3 3 4 2 3 3 3 4 4	4 3 3 4 3 3 4 4 2 3 2 2
	Fuchsin	2 3 3 3 3 4 4 4 4	4 3 3 3 3 3 2 2
11	Iodine vapor	2 2 2 2 3 3 4 3 4 3	2 3 3 2 2 2 2 2 2 2 2 2
	Fuchsin	2 2 3 3 3 4 4 4 4	3 3 3 3 3 2 3 2

TABLE VII. SODIUM ESTRONE SULFATE—ORAL 1.25 MG. DAILY FOR EIGHT DAYS

PATIENT	STAIN	SODIUM ESTRONE SULFATE	
21	Iodine vapor	2 2 2 2 3 1 3 2	4 3 2 3 3
	Fuchsin	2 2 2 3 3 3 4 4	
22	Iodine vapor	2 2 2 2 2 3 3 3	4 4 4 4 4
	Fuchsin	2 2 2 3 3 3 4 4	
24	Iodine vapor	1 1 1 2 2 2 2 2	3 2 2 2 2
	Fuchsin	1 1 1 2 3 3 3	

Comment

Inspection of Table I shows no essential or significant vaginal epithelial changes associated with the administration of thyroid. Such was to be expected since there is little or no evidence that thyroid extract has any estrogenic effect, at least, for the short period of medication and observation in this test. These first three cases, then, may be regarded somewhat as controls. On the other hand, all the estrogenic substances caused marked changes both in the glycogen content and in the fuchsin stainable cytologic features. Variations in the cellular glycogen were interpreted in the article previously mentioned,[4] and therefore the discussion here need be largely concerned only with a comparison of the two staining methods.

As a check on the grading of the two methods, the earliest duplicate smears were compared. They came on the first or second days of medication and before there could have been any substantial effect from the treatment. These initial duplicate smears from the 21 women showed the identical grade or reaction in 14. In 5 instances, the iodine vapor smear was one grade higher, and in 2 it was lower.

Since Willson and Goforth[6] reported the reaction from diethylstilbestrol to be evidenced by an increase of the glycogen in advance of other cell alterations, it was thought that the same relationship might hold for the maximum reaction which would follow treatment with estrogenic substances. Actually, this tendency proved to be the case in only one-third of the 18 cases; whereas in 9, or one-half, the maximum change was evidenced first in the fuchsin preparations. In the remaining 3, the greatest reaction was noted by both methods on the same day. Regarding stilbestrol itself, it will be seen that our 3 postmenopausal women given this substance first showed the maximum reaction with the iodine vapor technique, by the fuchsin method, and in both smears at the same time in one instance each.

Of some importance, especially regarding the treatment of vaginitis, would be any difference for the two methods in the duration of the reaction obtained from the administration of estrogenic substances. For the 12 patients who had enough duplicate smears to permit estimation (Tables II, III, IV, and VI), there was no important difference in the number of days at the maximum reaction resulting from treatment, there being 67 days with the fuchsin smears and 63 with those stained for glycogen. It is also noteworthy that, in spite of variations in time of incidence as mentioned in the preceding paragraph, an equal degree of smear reaction was reached sooner or later with both methods in 9 of these 12 cases. In 2 of the remaining 3 women the fuchsin smears, and in the last instance those stained by iodine vapor failed at any time to attain the highest grade found by the other method.

In conclusion, then, it can be said that these comparisons indicate no constant or significant differences in grading or reaction for duplicate

vaginal smears stained by fuchsin or iodine vapor methods in untreated menopausal women, or after the adminstration of thyroid gland and various estrogenic substances. Therefore, in view of its rapidity and simplicity, the iodine vapor stain for glycogen appears to deserve previous recommendations.

Acknowledgment is made to Dr. Harold C. Mack for his kindness in permitting use of his material and for suggestions regarding the conduct of these comparisons.

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955 FISHER BUILDING

EXPERIENCE WITH THE SIX HOUR RAT TEST FOR PREGNANCY*

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INNUMERABLE pregnancy tests have been described in medical literature. Most of them have one or more disadvantages which have kept them from being generally accepted. It was not until Aschheim and Zondek described their technique that there became available a pregnancy test which met most of the requirements for such a procedure.

A pregnancy test, in order to be of much value, must meet certain specifications: its degree of accuracy must approach 100 per cent; it must be reasonably rapid and relatively simple.

To meet these requirements, much experimental work has been done. It would seem that the ideal test should be a chemical one, thus removing the source of error inherent in all work which depends upon biological assay.

Last year, Salmon and Geist[1] and their associates at the Mount Sinai Hospital used, as a pregnancy test, an observation which had been made many times before. They reported that within six hours after the injection of the urine of pregnant women into suitable rats a definite erythema of the ovaries developed. This was constant and their results compared favorably with those obtained with the Aschheim-Zondek or Friedman tests. In our laboratory, in 107 cases, we have had the same experience.

Technique

Female rats are used as the test animals. They must be about four weeks old and weigh about 30 grams. Since these animals have a spontaneous estrus cycle and ovulate spontaneously at maturity, they cannot be used when they become much larger. Two animals are employed and two cubic centimeters of urine are injected subcutaneously into each. After six hours, the animals are asphyxiated with illuminating gas. In positive cases, the ovarian hyperemia is manifested by a reddening of the ovary. This redness is grossly visible in good light. Usually the uterus, too, is edematous and red looking although the interpretation of the test depends on the ovarian and not the uterine conditions. In the negative cases, the ovaries are small and white and the uterus is a white, threadlike structure.

In 107 cases, the following results were obtained:

*Presented at a meeting of the Brooklyn Gynecological Society, October 1, 1943.

RESULTS IN PREGNANT WOMEN

	RAT TEST			FRIEDMAN TEST		
	TOTAL	POSITIVE	NEGATIVE	TOTAL	POSITIVE	NEGATIVE
1st trimester	39	37	2 (a, b)	20	18	2 (b, c)
2nd trimester	2	2				
3rd trimester	13	13				
Duration unknown	9	9				
Total	62	61	1	19	18	1

(eliminating dead fetus case)

a—Test in rat negative but Friedman test positive. Clinically the patient was shown to be pregnant.
b—Both rat and Friedman test were negative. In this case the fetus had been dead for about 3 months.
c—Friedman test negative but rat test positive. This patient was shown to be pregnant clinically.

RESULTS IN NONPREGNANT WOMEN AND IN MALES

	RAT TEST			FRIEDMAN TEST		
	TOTAL	POSITIVE	NEGATIVE	TOTAL	POSITIVE	NEGATIVE
Males	15	0	15	0	0	0
Nonpregnant Women	29	1 (d)	28	9	0	9
Totals	44	1	43	9	0	9

d—As this was one of the early cases, the error may have been due to inexperience in interpreting the findings.

Comment

At the beginning of the study, samples of urine were tested from male students, known pregnancies and known nonpregnancy cases. The identity of the subject was not known to the individual reading the result. Later, rat tests were done on the urines submitted for routine Friedman tests and the readings were made before the Friedman tests were completed. In those cases where there was no Friedman test and the samples were received from an outside source, follow-up was requested on the basis of the clinical course. In this way it is felt that all possible sources of error have been covered.

After this careful investigation it was found that 61 women out of 62 who were definitely pregnant gave a positive rat test while in one the test was negative. In 19 of these pregnant women the Friedman test was also done with 18 positive and one negative result. It is interesting to note that in the instance in which the rat test was negative, the Friedman test was positive, and in the case in which the Friedman test was negative, the rat test was positive. One patient in whom the fetus had been dead for three months gave a negative rat test and Friedman test.

In 44 instances in which there was no pregnancy, 43 rat tests were negative and one was positive. In 9 of these in which the Friedman test was also done, no positives were obtained. It may be possible that the positive rat test which was obtained in a nonpregnant woman was due to inexperience in interpreting the findings since this was one of the early cases.

Certain technical and economic details may be mentioned. Since the rats are of value for a very short span of their life (about two weeks) it is necessary to have a large colony on hand so that young are always available. If possible, the results should be read in daylight since color determinations are notoriously difficult under artificial light. And it is well to be sure that the individual making the readings is not color blind. For this reason, women often do better than men.

In conclusion we feel that, although the number of cases reported is not large enough to warrant an absolute statement as to the value of this test, enough work was done and the results were sufficiently accurate to justify the assumption that this may prove to be a valuable addition to our laboratory tests for pregnancy. It certainly warrants further trial by ourselves and others. Although it does not obviate all the difficulties inherent in biologic testing, this method shortens the time from some 36 or 48 hours down to six hours.

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VOLVULUS OF CECUM AS A POST-PARTUM COMPLICATION

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LITTLE can be found in American medical literature associating volvulus of the cecum with pregnancy. The enlarging gravid uterus has been known to precipitate volvulus. An article appearing in the *British Medical Journal* for October 25, 1941, p. 577, presents the case history of a patient succumbing to volvulus of the cecum following a difficult high forceps delivery in a 38-year-old primigravida. The diagnosis was made at autopsy. The author called attention to the fact that surgeons are reluctant to resort to surgical intervention during the puerperium and that abdominal complications are accordingly neglected. He further stated that pelvic peritonitis, retroperitoneal hemorrhage, paralytic ileus, and abdominal castrophes such as volvulus, all may produce abdominal distention and be found as post-partum complications.

A case of volvulus of the cecum, as an unusual post-partum complication, was currently observed in the family outpatient department of the U. S. Naval Hospital, Philadelphia. A primigravida, 33 years of age, presented herself in the dependent clinic on March 31, 1943. Her last menstrual period had occurred on October 25, 1942, the estimated date of confinement being August 2, 1943. Family history was noncontributory. The patient had typhoid fever at the age of 18 years. Gastrointestinal history revealed the presence of an obstinate constipation which had largely subsided after the second month of pregnancy. The prenatal course preceding her first visit to the dispensary had been normal.

The patient was a small, well-developed and well-nourished white woman of German extraction. Her usual weight had been 112 pounds. There was a weight gain of ten pounds the first five months of pregnancy. General physical examination was negative. The abdomen was enlarged to the size consistent with a five months' pregnancy and the uterus was in the midline. Pelvic measurements were considered to be adequate for a vaginal delivery.

The prenatal course was uneventful until the eighth month when the patient developed a mild pitting edema of the extremities. The laboratory examinations were consistently normal. The weight gain continued to 134 pounds, or a total weight gain of 22 pounds.

The patient was admitted to the family out-patient obstetrical floor at St. Agnes Hospital at 6:30 A.M. on July 21, 1943. Pains had begun three hours before and the head was deeply engaged in the left occiput posterior position. The head rotated spontaneously to an anterior position and a low forceps delivery was completed at 10 A.M. The placenta was expressed intact with an estimated blood loss of 300 c.c.

Reaction to delivery and anesthesia was normal and the patient was comfortable until 9:30 P.M. the day of delivery. At this time there was upper and lower abdominal distention which was relieved by rectal tube

*The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Navy Service at large.

and the removal of 500 c.c. of urine by catheter. The patient rested comfortably the remainder of the night. The morning of the first post-partum day the patient again complained of upper abdominal pain which was again relieved by rectal tube and the administration of one ampule of prostigmine. Temperature, pulse, and respiration were normal and the patient was still unable to void. By 11:00 P.M. of this day the patient again complained of severe upper abdominal pain. There was a soft, upper abdominal distention and the abdomen was not tender. Hot abdominal stupes were applied and a soda bicarbonate enema administered. This resulted in the passage of stool and flatus and relief of pain.

On the morning of the second post-partum day there was a moderate upper abdominal distention, but the patient was retaining fluids by mouth, expelling flatus, and temperature and pulse were normal. She was still unable to void. One ounce of castor oil was administered by mouth and four hours later there was a copious bowel movement with a reduction in the distention, and an almost complete relief of pain. One hour later, and for the first time since delivery, the patient vomited some undigested food. By 9:30 P.M. the distention had recurred and a consultation was requested from the surgical service of the U. S. Naval Hospital. Paralytic ileus and partial mechanical obstruction were considered to be tentative diagnoses. The patient was still afebrile; pulse rate of 80. Wangensteen suction was instituted and three units of plasma administered.

A flat plate of the abdomen taken on the morning of the third post-partum day was not entirely satisfactory because of gaseous distention, but it revealed a large bowel distention with no definite point of obstruction. Examination of the abdomen showed some visible peristalsis. Five hundred c.c. of citrated blood were administered. Following this the patient had a chill and temperature elevation to 103.5° F. Temperature returned to normal four hours later and the supposition was that the chill and fever represented a transfusion reaction. Distention remained moderate throughout the day.

On the morning of the fourth post-partum day, the distention was definitely accentuated, the abdomen was tender, no peristalsis could be discerned by auscultation and the patient's condition was obviously more critical. Temperature was mildly elevated and the pulse rate was increased.

At 2:00 P.M. on the fourth post-partum day, operation was done under continuous spinal anesthesia. The abdomen was entered through a small left rectus incision revealing a hyperemic peritoneum and an increase in intraperitoneal fluid. A huge sausage-shaped mass could be felt extending obliquely upward and to the left across the abdomen. As the incision was enlarged, a volvulus of the cecum and lower portion of the ascending colon spontaneously delivered itself. The mesocolon was edematous and definitely elongated and the bowel had rotated counterclockwise, allowing the cecum to occupy a position beneath the left lobe of the liver. The bowel was dusky, there were some breaks in the serosa, but no evidence of devitalization. Reduction of the volvulus was easily accomplished and cecostomy was performed, the cecostomy tube being carried out through a stab wound in the right lower quadrant. The abdomen was closed without drainage after the introduction of five grams of sulfathiazole crystals. Three units of plasma were given and the immediate postoperative condition was excellent.

Wangensteen drainage was continued. Intravenous sodium sulfathiazole was administered at eight-hour intervals, and plasma, citrated blood, and intravenous glucose solution were given. The patient was irrational on the first and second postoperative days. There was a mild jaundice which was thought to be hemolytic and associated with the transfusions. Maximum temperature elevation reached 103.4° F. The Wangensteen tube was removed on the third postoperative day, and the colostomy tube and all sutures were removed by the fourteenth postoperative day. The patient was discharged from the hospital on the twentieth postoperative, or the twenty-fourth post-partum day. Her bowel habits had been normal for one week at the time of her discharge.

This case constitutes an unusual complication following a normal delivery. We feel that delivery with the sudden emptying of the uterus was a contributory factor. A partial obstruction probably existed from the time shortly following delivery, becoming complete on the evening of the third post-partum day. It is conceivable that an exact diagnosis could have been arrived at preoperatively, and surgical intervention instituted at an earlier date.

CURE BY PENICILLIN FOLLOWING REPEATEDLY UNSUCCESSFUL SULFONAMIDE THERAPY IN A PREGNANT WOMAN WITH GONORRHEA

HYMAN STRAUSS, M.D., BROOKLYN, N. Y.
(From the Kingston Avenue Hospital of the Department of Hospitals)

PENICILLIN therapy has already been reported in a large series of cases by various investigators. In this country, Keefer and his associates have published a notable series covering a variety of infections. Their report included 129 gonorrheal cases treated by Mahoney and his associates in the United States Public Health Service, seventy-five of which have already been reported. To date Mahoney and Van Slyke have treated 179 cases.

It is, therefore, with humility that I present this single patient but I feel justified in doing so because the case has certain unusual aspects and was most carefully checked culturally and clinically during and after treatment. The report is also unique in that there was no alternative therapy possible. We know of no similar case noted in such detail.

F. C., female, white, single, nullipara, 21 years of age, was admitted to the Kingston Avenue Hospital April 16, 1943, pregnant six and one-half months, with a cervical culture positive for the gonococcus. The cervical smear was negative. Urethral smear and culture were negative, as was the blood Wassermann.

The findings after admission, however, disclosed a profuse purulent urethral discharge with smears and cultures positive for the gonococcus. Skene's ducts were thickened. The left Bartholin's gland was the size of a cherry, while the right was normal. Condylomata accuminata about a quarter of an inch in diameter were present on the labia majora. The vaginal walls were inflamed and trichomonads were found in the discharge. The cervix was bluish with small erosions on both lips. There was a profuse mucopurulent discharge which disclosed gonococci on both smear and culture. The uterus was soft and enlarged to two fingers-breadth above the umbilicus, and the fetal parts were easily outlined. Urine analysis, blood count and sedimentation rates were normal.

On the day following admission she was started on a course of sulfathiazole. This consisted of four grams of the drug given daily for seven days. Lactic acid douches were given for her trichomonas infection. On April 26, and 28, gonococci were found in smears and cultures of the urethral and cervical discharges. Clinically, the urethritis and cervicitis showed no improvement.

On May 5, she was started on a course of four grams of sulfadiazine and sixteen grams of sodium bicarbonate daily for four days. Gonococci persisted in both the urethra and cervix and the clinical picture was unchanged.

On May 13, she was given three grams of sulfapyridine daily for ten days. The urethritis and cervicitis persisted and gonococci were still found in cultures from each.

Having failed to effect a cure with sulfathiazole, sulfadiazine and sulfapyridine and fever therapy being contraindicated because of the pregnancy, it was decided to administer penicillin. We were fortunate

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Having failed to effect a cure with sulfathiazole, sulfadiazine and sulfapyridine and fever therapy being contraindicated because of the pregnancy, it was decided to administer penicillin. We were fortunate

to secure 88,000 Oxford units.* On June 9, administration of the drug by continuous intravenous drip was begun. Penicillin (8800 units) were dissolved in 1,000 c.c. of normal saline and repeated every six hours. The intravenous administration was continued over a period of sixty hours. The patient was kept on a soft diet and fluid intake and output were charted. Temperature, pulse and respiration remained normal. Cultures and smears were taken from the cervical and urethral discharges at 3- to 6-hour intervals during the penicillin treatment. In three hours, after 4,400 Oxford units of penicillin had been given, the first cultures were taken and found to be negative. Thereafter sixteen consecutive cultures and smears from both the urethra and cervix remained negative. Clinically, the patient improved and ten days after completion of penicillin therapy, she was sent home free of gonococcus infection. The cervical erosions were also almost completely healed.

On July 4, she was admitted to another hospital at term in active labor. Twenty-two hours later she was delivered spontaneously of a normal female infant weighing 5 pounds, 12 ounces. Puerperium was uneventful. Smears and cultures taken from the baby's eyes were negative for gonococci.

On August 11, 23, 25, and September 8, the patient returned for post-partum checkups. She showed the usual post-partum findings, with no evidence of gonorrhea. Cultures and smears from both urethra and cervix were negative at these times making a total of twenty consecutive cultures and smears.

Comment

This patient was refractory to sulfathiazole, sulfadiazine and sulfapyridine. Fever therapy was considered to be contraindicated because of the risk involved. She responded dramatically to penicillin and remained culturally and clinically free of the disease despite the provocation of delivery. The child likewise showed no evidence of infection.

Although this is but a single case and one hesitates to draw conclusions, it is quite possible that further experience will disclose that smaller dosage is effective in gonorrhea. Extensive studies on the use of penicillin in sulfonamide refractory individuals has so far been limited to the male. It is well known that the more scientific study in gonorrhea resolves itself about the female who is the principal disseminating factor of the infection. Moreover, the presence of such naturally occurring provocative tests as menstruation and pregnancy enhance the value of female studies. It is hoped that the means will soon be available for such clinical evaluation.

Penicillin therapy was effective in producing a rapid laboratory and clinical cure of a sulfonamide-refractory pregnant individual, in whom fever therapy was contraindicated. The baby likewise was free from infection.

755 Ocean Avenue

*The penicillin was furnished by Charles Pfizer & Company, Brooklyn, N. Y.

VULVAR EDEMA COMPLICATING DELIVERY

NATHAN BLOCK, M.D., NEW YORK, N. Y.
(From the Department of Obstetrics, Sinai Hospital of Baltimore)

EDEMA of the vulva may occur at any time during pregnancy, but, except in labor, it is more of an annoyance than a complication. It is almost invariably associated with generalized anasarca, with cardiac or renal disease, with hepatic disease involving obstruction of the portal circulation, or with pathological conditions causing pressure on the venous return. The degree of involvement varies considerably. Occasionally, when of prolonged duration, gangrene has occurred.

The treatment is that of the underlying pathology. The patient should be given a complete physical examination, and then proper corrective measures should be instituted. Local treatment is mainly bed rest, preferably in the Trendelenburg position, to decrease the intra-abdominal pressure on the affected venous circulation. Hot applications to the perineum may be of some value.

Vulvar edema is rarely a serious complication of labor because the amount of swelling does not reach sufficient proportions to cause a soft part dystocia. If some obstruction is created, scarification or a deep episiotomy usually overcomes it. Asepsis must be strictly observed as secondary infection of the traumatized tissue is not uncommon.

The following case is reported to illustrate the extreme degree of this condition.

I. G., a 24-year-old, unmarried, white multipara, was admitted to the obstetric ward of Sinai Hospital for observation on March 27, 1943. She was a nonclinic patient, and had not received prenatal care. A previous pregnancy, 2 years ago, complicated by a severe pre-eclamptic type of toxemia, was terminated successfully by medical induction of labor and low forceps delivery of a living child.

For 10 days at home, the patient watched "swelling" develop in her lower extremities before consulting a doctor, who advised immediate hospitalization. On admission, the lower extremities were found to be very edematous, but the striking feature was the phenomenal size of the labia majora. The abdomen was so edematous that no accurate palpation of the fetus was possible. There was no history of headache, visual disturbances, nausea, or epigastric pain. Blood pressure was 150/180. Examination of the eye grounds showed a few tortuous vessels, slight overfilling of the veins, but there was no spasm of the arteries. General physical examination was negative except for the presence of aortic insufficiency. The lungs were clear. The liver and spleen were not palpable. The urine consistently showed 4-plus albumin (3 to 4 Gm. per 24-hour specimen). Output was poor; only 475 c.c. in 24 hours. Blood counts and chemistry were normal except for total proteins 5.1; serum albumin 2.6 per cent; serum globulin 2.5 per cent.

Fluids were limited to 1,000 c.c. daily. She was given 200 c.c. of 25 per cent glucose intravenously every four hours and one ounce of magnesium sulfate by mouth each morning. Two 500 c.c. plasma transfusions were administered in the hopes of raising the serum proteins. Despite this therapy, she excreted increasing amounts of albumin, the urinary output became dangerously low and her blood pres-

sure rose steadily until it reached a peak of 190/110 on the third day of hospitalization. The vulva had attained such proportions by this time that a severe degree of soft part dystocia was present. The labia were discolored, very tense, and it was impossible to part them (Fig. 1). Gangrene of the skin was feared, and the decision to interrupt pregnancy was inevitable. Cesarean section was decided upon as the procedure of choice after trial aspiration with a syringe had produced a negligible amount of fluid. Very extensive scarification of the skin would have been necessary in order to rupture the membranes, and then it would have been too doubtful that the obstruction could be overcome sufficiently to permit vaginal delivery.

Fig. 1.—The vulvar edema preoperatively. Note involvement of perineal body and rectum.

Under cyclopropane anesthesia, a low cervical cesarean section was performed. A living child was delivered and also an undiagnosed twin. Both children were in good condition. The patient withstood the operation very well, and had an almost afebrile postoperative course. The generalized edema was gone in three days, and the vulva showed marked improvement. At the time of discharge, the edema had completely disappeared. The patient and the babies were discharged on the sixteenth day in good condition. She had lost a total of 42 pounds during her stay in the hospital.

MEIGS' SYNDROME

EDWARD KELEMEN, B.A., M.D., LONG BRANCH, N. J.
(From the Monmouth Memorial Hospital)

THE following case report illustrates clearly the need for a more widespread recognition of Meigs' syndrome. In this case the diagnosis was made preoperatively, but only after a dangerous delay, prolonged study and an accidental recognition of the condition.

Mrs. E. G., entered the medical service at the Monmouth Memorial Hospital on July 2, 1942. Her chief complaints were cough, dyspnea, weakness and diaphoresis. Her gastrointestinal, genitourinary and cardiovascular past history was negative. No history of tuberculosis could be elicited.

A physical examination revealed a well-developed, thin, forty-nine-year-old, white female lying on her right side. Temperature 100° F., pulse 108, and respiration 32. Respirations were rapid and shallow, the skin pale, cool and dry. Head and neck were negative. The right chest contained fluid up to the apex. The heart was shifted far to the left. The distended abdominal cavity contained fluid and an irregular, hard and movable mass measuring roughly 20 by 15 cm. and extending from the symphysis pubis to the umbilicus. Pelvic examination, carried out advantageously only after the removal of 5,500 c.c. of clear, serum-colored fluid, revealed an ovarian mass which was freely movable. A pigmented nevus was present on the mons veneris. The extremities were negative. Blood, Wassermann and Kahn tests were negative, the blood count normal. Blood urea nitrogen, blood sugar and serum protein were also at normal levels. Fluid from the right pleural and abdominal cavities was of a specific gravity of 1.012 and sterile. Chest roentgenograms revealed no evidence of pulmonary tuberculosis.

Surgical and medical opinion were agreed that this case represented a papillary adenocarcinoma of the ovary with pleural metastases, and therefore, advised against exploratory laparotomy.

A diagnosis of Meigs' syndrome was made by the writer following a delay of almost 12 weeks, during which time 43 liters were removed from the pleural and abdominal cavities, the fluid at all time being sterile and transudate in character.

On September 30, 1942, under sodium-pentothal anesthesia, Dr. Harold Kazmann removed an ovarian fibroma. The specimen was hard, irregular and nodular and measured 15 by 8 by 12 cm. Microscopic examination revealed that "the tumor is composed of fibroblasts, closely placed, forming a cellular structure. Nuclei are large and pale, but not anywhere do they show evidence of malignancy. Throughout the tumor are small masses of cells of another character, mostly poorly preserved, but here and there are seen epithelial cells uniform in structure with small, dark nuclei. Such masses have developed cystic spaces in many instances. The epithelial inclusions serve to identify this as a Brenner tumor, in many of which, the development of fibrous tissue is such as to almost entirely obliterate the elements. Such a tumor as this is, in consequence, essentially a benign fibroma. It is quite consistent with Meigs' syndrome.

Pathological Diagnosis: Brenner's Tumor.—The patient made an uneventful convalescence, was discharged and followed up as cured during the last eleven months.

This case is presented primarily because the underlying pathology was a Brenner's tumor.

CHIARI'S SYNDROME

J. Craig Potter, M.D., Rochester, N. Y.

CHIARI in 1855 reported two cases of a syndrome which has occurred very rarely. It consists of amenorrhea with persistent lactation following delivery. In 1882 Frommel found one case in a study of 3,000 gynecological patients in Vienna. Sharpe[1] in 1935 reviewed the literature, finding in all, four papers on the subject.

As the condition is so rare and as none of the reported cases had a subsequent pregnancy, the following case seems worth recording.

Mrs. F. J., aged 32, was seen July 17, 1934. At the age of 23, an ovarian cyst was removed and an appendectomy done. In 1933, she was delivered by low forceps and episiotomy of a full-term baby girl weighing 8 pounds and 3 ounces. She did not menstruate following the delivery and her breasts continued to lactate. In 1934, desiring another child, she was sent to me by Dr. Mac Naughton Wilkinson for study and to determine, if possible, the cause of the amenorrhea and lactating breasts. The physical examination was negative except that the breast ducts were full of secretion and the uterus was atrophic. Routine laboratory tests, including a basal metabolism, were negative. Endometrial biopsy revealed an atrophic endometrium. The endocrine preparations of that day were tried without relief. They were thyroid, progynon in oil, and corpus luteum extract.

In 1941, the patient returned, stating that in 1940, her breasts had stopped secreting and her periods had returned. Her weight, 142 pounds was the same. The question was, could she become pregnant? However, on January 20, 1942, Mrs. F. J. came to the office having missed two periods. Examination showed a pregnant uterus but the breasts were not secreting.

On September 7, 1942, she was delivered of a 9-pound baby girl by the Bell modification of the Scanzoni maneuver. She was unable to nurse the baby because of insufficient milk. To date, November 2, 1943, she has not menstruated and her breasts are dry.

As far as I know, this is the only patient with Chiari's syndrome who has had a subsequent pregnancy and delivery. An x-ray of the sella turcica and sugar tolerance test would have been interesting, but there was nothing clinically to suggest difficulty in the pituitary gland.

Reference

1. Sharpe, E. A.: Frommel's Disease, Am. J. Obst. & Gynec. 30: 411-414, 1935.

Department of Reviews and Abstracts

Selected Abstracts

Vaginal Infections

Perez, Manuel Luis, Arenas, Normando, and Blanchard, Oscar: Our Experience in the Treatment of Vaginal Trichomoniasis, An. Inst. de Mat. y Asist. Soc. 2: 63, 1940.

Manuel Luis Perez, Normando Arenas and Oscar Blanchard review the methods of treatment in general use for trichomonas vaginalis vaginitis. They found the infection in 32 per cent of nonpregnant women, and in 50 to 70 per cent of pregnant women. Of all the pentavalent arsenicals used the most successful was p-oxy-acetylamino-phenylarsenic acid with kaolin as a vehicle. The instillation of 2 Gm. of the drug is preceded by vaginal application of a solution of 1 per cent picric acid. Good results were obtained in 150 patients. There were no recurrences. The authors also used silver picrate, 0.5 Gm. to 3 Gm. of kaolin, to which they added suppositories of silver picrate during the first week. The treatments were repeated every five to seven days and most patients were cured after from four to six applications.

J. P. GREENHILL.

Brady, Leo, and Reid, Roger D.: The Treatment of Trichomonas Vaginalis Vaginitis With Lactobacillus, Ann. Surg. 115: 840, 1942.

The authors present a method in the treatment of a very common ailment. They do not feel that the discharge of trichomonas vaginitis is typical to any degree, but it can simulate any other type of vaginal discharge. Failures in diagnosis may be attributed to the fact that sometimes the condition is overlooked and, secondly, that a previous bimanual examination with some lubricant inactivates the protozoan. Another failure in diagnosis may be attributed to the preliminary douche before examination. It is the opinion of the authors that not only is acid therapy necessary, but that lactobacilli are also essential. A method was worked out whereby the authors inoculated sterile skimmed milk with lactobacillus bulgaricus and mixed it with sugar and milk sugar in such a manner as to form tablets. These tablets are then inserted into the vagina. The authors treated 50 cases in such a manner from 3 to 6 weeks and longer when necessary, with recurrences in only six cases. The relief is rather prompt. The importance of treatment for a few days each month around the menstrual time is stressed.

WILLIAM BERMAN.

Menopause

Bennett, Henry G., Jr., and TeLinde, Richard W.: The Menopausal Syndrome, J. A. M. A. 118: 1341, 1942.

The authors describe their method of treatment of the menopause symptoms with the use of pure crystalline estrogen converted into pellets by compression of the substance in drilled machine ground steel plates. The number of implantations number from one to five and the average total weight of estrogen in each implantation was 40 milligrams. Ninety-three and four-tenths per cent considered the above treatment satisfactory. Improvement usually began within two weeks

following implantation and lasted an average of 16.2 weeks. There were no signs of toxic or systemic reaction. One case of abnormal uterine bleeding was encountered. The method compares favorably only with that of the injection of stilbestrol pellets subcutaneously, except that with the latter, the side reactions are more marked.

Another group of patients with theelin crystals in aqueous suspension administered hypodermically in total doses of 5 to 25 milligrams and satisfactory clinical results were obtained in only 59.3 per cent of twenty-seven patients. Oral natural estrogens given three times daily by mouth produced satisfactory results in only 46 per cent of the cases.

Patients in the acute phase of the menopause respond better than those with prolonged histories. Surgical castrates responded better to pellet implantation than either the irradiated or the physiologic group. In regards to the vaginal smear, it was found that symptomatic relief preceded any change in the vaginal smear. There was no evidence to indicate that the estrone pellets were responsible for bleeding in this group. No evidence of benign endometrial proliferation was noted when pellets of estrone were used, but this was noted when the diethylstilbestrol pellets were used. There is some evidence to indicate that estrone is the weakest growth stimulator of the various estrogens.

WILLIAM BERMAN.

Freed, S. C., Wisin, W. M., and Greenhill, J. P.: The Oral Effectiveness of Estrone Sulfate (Conjugated Estrogens-Equine) in Women, J. Clin. Endocrinol. 3: 89, 1943.

Estrone sulfate (premarin) is a naturally occurring estrogen in the urine of pregnant mares. According to laboratory evidence, it is several times more potent than free estrone by mouth when administered to spayed rats. Administered to 152 women in dosages of 1.25 mg., 0.81 mg., and 0.4 mg., three times daily, it was found through therapeutic standardization according to subjective response to be satisfactorily effective in relieving symptoms of the menopause. Optimal results were obtained with the higher dosage, while the lower dosage generally resulted in the relief of symptoms. The results obtained were generally superior to those obtained in comparison with 118 women who received daily 0.5 mg. and 1.0 mg. of diethylstilbestrol orally.

CLAUDE J. EHRENBERG.

Glass, S. V., and Rosenblub, Gordon: Therapy of the Menopause. Superiority of Conjugated Estrogens-Equine Over Diethylstilbestrol, J. Clin. Endocrinol. 3: 95, 1943.

Previous to the introduction of sodium estrone sulfate (premarin) climacteric patients were treated orally with estriol glucuronidate (emmenin) and diethylstilbestrol. Introductory treatment in the severe cases with parenteral estrone or estradiol was frequent. In a preliminary study, eighty patients were administered sodium estrone sulfate with supplementary doses of diethylstilbestrol. The latter drug was soon found to be unnecessary for complete symptomatic relief.

The present report is based on the treatment of seventy-one menopausal patients with sodium estrone sulfate alone. Initial dosages of 2.5 mg. to 3.75 mg. daily which were gradually reduced to as low as 1.25 mg. three times weekly effected good results in 82 per cent of the cases, fair results in 10 per cent, and poor results in 8 per cent of the patients. Questionable complications were noted in two cases. Sodium estrone sulfate is safe, effective, and orally active therapy for the relief of climacteric symptoms.

CLAUDE J. EHRENBERG.

Sevringhaus, Elmer L., and St. John, Ruth: Oral Use of Conjugated Estrogens-Equine, J. Clin. Endocrinol. 3: 98, 1943.

An attempt to secure a more potent water-soluble and conjugated estrogen has led to the production of Premarin. Although for clinical usage, it is unnecessary to reduce the compound to a state of crystalline purity, standardization must be made with reference to purified estrone sulfate.

Genuine estrogenic potency of the material administered orally in dosages of 1.25 mg. to 5 mg. daily was demonstrated through the use of vaginal smears from eighteen menopausal women of whom nine were artificially induced by bilateral oophorectomy. Further evidence of this potency was indicated by the occurrence of uterine bleeding in two of the patients.

Symptomatic relief of climacteric symptoms was complete in twenty-two of twenty-five patients to whom the substance was given orally. Of the three patients without relief, other reasons seemed to account for the failure.

Comparison of the above results with use of the other estrogens in the same women was made in an attempt to determine the relative value per dollar cost to the patient. Although the comparisons did not result in definite equations, it could be stated that estrogens-equine were as effective per dollar as the other natural estrogens according to 1941 retail prices. Further, 1.25 mg. of estrogens-equine is at least as potent as 2,000 I.U. and may be better than 5,000 I.U. of estrogenic substances, and is as effective as 1 mg. of diethylstilbestrol.

CLAUDE J. EHRENBERG.

Gray, Laman A.: Clinical Study of a New Type of Estrogen Preparation for Oral Use, J. Clin. Endocrinol. 3: 92, 1943.

Premarin, a new type of natural estrogenic preparation, consists of the natural conjugated estrogens of pregnant mare's urine. The predominating estrogen is estrone sulfate and standardization is expressed in milligrams as such. The result of treating sixty-four menopausal women was gauged on the basis of symptomatic improvement and changes in the vaginal smear. Dosages were 1.25 mg., 0.62 mg., and 0.31 mg. daily by mouth. Symptomatic improvement and vaginal epithelial response was generally better with the highest dosage; 1.25 mg., administered daily for 7 days, and thereafter that amount every other day, gave as complete symptomatic relief for the usual menopausal symptoms as could be obtained with other types of estrogenic therapy, and produced a vaginal growth effect equivalent to that of diethylstilbestrol mg. for mg. Complications were relatively few, one patient experiencing nausea, and four patients experiencing uterine bleeding during the course of treatment.

CLAUDE J. EHRENBERG.

Breasts

Speert, Harold: "Pale Epithelium" in the Mammary Gland and Its Experimental Production in the Rhesus Monkey, Surg., Gynec. & Obst. 74: 1098, 1942.

The author reviews the literature on "pale epithelium" in the mammary gland. In a study of 474 breasts obtained from 304 rhesus monkeys, five instances of atypical epithelium, resembling "pale epithelium" are reported. These all occurred in a special group treated with large amounts of estrogen, and 4 out of 5 were in castrates. The author is of the opinion that these pale cells represent metaplasia of normal mammary epithelium. These cells probably play no part in the development of carcinoma.

Bucher, N. L. R., and Geschichter, C. F.: Pregnandiol and Estrogen Output in the Urine of Patients With Chronic Cystic Mastitis, J. Clin. Endocrinol. 1: 58, 1941.

The term chronic cystic mastitis has been used for decades to denote a benign lesion of the breast which is neither inflammatory nor neoplastic. Recent studies indicate that the changes in this disease are associated with endocrine disturbance.

Chronic cystic mastitis or mammary dysplasia comprises three groups of cases. Mild or early cases with painful dense mammary tissue are usually referred to as painful breasts or mastodynia. Cases with more persistent and definite nodularity are referred to as adenosis, shotty breast or Schimmelbusch disease, after Schimmelbusch, who described microscopically the proliferative changes in this condition. The third group of cases known as cystic disease is usually unrelated to the other two groups. It is characterized by development of one or more cysts of appreciable size in women whose breasts were previously normal.

Nancy L. R. Bucher and Charles F. Geschichter (Johns Hopkins Univ.) report endocrine studies on a group of cases of chronic cystic mastitis. The group includes seven cases with mastodynia, five cases with adenosis, and four cases with cystic disease. The urine of the twenty-three patients was assayed for pregnandiol excretion, and for twelve of these patients estrogen excretion was also determined.

The endocrine disturbances in mastodynia and in adenosis are similar. Adenosis may be looked upon as a more advanced stage of mastodynia. This is borne out by the clinical histories. Nearly all patients with adenosis give a history of painful breasts. Although the majority of cases with mastodynia, when followed for a period of five to ten years, show spontaneous regression, a small group develop adenosis during such a period of time. In a series of 241 cases of mastodynia followed for more than five years, ten cases (5 per cent) developed adenosis.

From an endocrine standpoint, both mastodynia and adenosis show corpus luteum deficiency. Estrogen values may be normal. From another point of view, cases with mastodynia and adenosis may be looked upon as having a relative hyperestrogen secretion. Experimentally this viewpoint is justified, since in castrated rats estrogenic stimulation alone with pellet implantations or daily injections of five to ten of estrone for several months, produces the characteristic picture of mastodynia and adenosis.

It is not possible to state with assurance the endocrine disturbance in cystic disease. The opinion based upon the few assays performed and the experimental production of cystic disease in animals is that the cysts develop following prolonged or intense unopposed estrogen stimulation, or after the withdrawal of a previous estrogenic stimulation.

J. P. GREENHILL.

Shinkai, T., Ohgusa, M., and Miyasaki, Y.: The Relation Between Supernumerary Breasts and Labor, Jap. J. Obst. & Gynec. 24: 34, 1941.

The authors maintain that women with well-developed supernumerary breasts seem to be prolific and have multiple pregnancies. Sterility among such women occurs half as often as in women without supernumerary breasts.

J. P. GREENHILL.

Warren, S.: Relationship Between Chronic Mastitis and Cancer of Female Breast, Rev. méd. de Rosario 30: 829, 1940.

Warren studied 1,044 cases of chronic mastitis in which a portion of the involved breast was microscopically observed. The patients included women with chronic simple and cystic mastitis, Schimmelbusch's disease, Semb's cystic fibro-

adenomatosis, Cheatle and Cutler's hyperplasia, Aschoff's cystic mastopathy and Reclus' disease. They were observed for an average period of nine years after operation. Cancer did not exist in any patient at the time of operation. It developed in thirty-five some time afterward. Warren found that the incidence of breast cancer was six times as great in women who had had chronic simple or cystic mastitis as in those who did not. It was greater in women above 30 and before the menopause than in those at the menopause or after. A relationship exists between chronic mastitis and development of cancer, although either condition may develop in the absence of the other. Treatment of chronic simple or cystic mastitis consists of excision of the involved portion of the breast. The patients should be observed for a long period after operation. The appearance of nodules or cysts in the remaining portion of the breast is an indication for unilateral mammectomy. Bilateral mammectomy is not justified as a preventive measure.

J. P. GREENHILL.

Pregnancy Complications

Hüssy, P.: The Sudden and Unexpected Deaths in Pregnancy and Labor, Schweiz. med. Wchnschr. **71:** 1283, 1941.

Sudden death during pregnancy and labor may occur as the result of eclampsia, particularly eclampsia without convulsions. Likewise, sudden death may occur as a result of acute pulmonary edema and acute yellow atrophy. Other causes of sudden death which have been described in the literature are hyperemesis, pyelitis, toxic myelitis, rupture of the uterus without symptoms, placenta accreta, hemorrhage from placenta previa, cervical laceration and rupture of varicose veins. Occasionally sudden death may result from abortion, hydatid mole, badly performed Credé manipulation, and pulmonary embolism. Furthermore, exitus may be brought about suddenly by affliction of the brain, particularly apoplexy, brain tumor and brain abscess. Occasionally sudden death is due to diabetes and other disturbances of the endocrine glands.

A certain number of deaths have been due to diseases of the heart and aorta. Likewise, rupture of the abdominal viscus has been responsible for some sudden deaths. Sudden death from shock is not infrequent.

J. P. GREENHILL.

Hughes, Edward C.: Hyperemesis Gravidarum, New York State J. Med. **42:** 1732, 1942.

The author describes pathologic changes encountered in cortical zone of three pairs of adrenal glands removed at autopsy in fatal cases of hyperemesis gravidarum. These changes went as far as hemorrhage and actual necrosis in places. Experimentally, similar conditions were produced in the adrenals of virgin rabbits following the injection of 60 c.c. of urine from patients suffering from hyperemesis. The thyroid also showed lower function in the experimental animals. Studies were carried out in normal pregnant women and those suffering from severe nausea and hyperemesis with the possibility of correlating the above findings with the metabolic changes encountered in normal pregnancy, and hyperemesis especially from the standpoint of fluid output and blood sodium levels. The author emphasizes the necessity of adequate intake of fluid, sodium chloride and glucose by mouth, or parenterally, if necessary. He recommends the administration of large amounts of vitamins B and C, and also the use of some form of adrenal cortical extract on account of the possible damage to the adrenals with consequent lowered adrenal function, and the resulting associated metabolic disturbances.

KARL M. WILSON.

Robillard, Gregory L., and Imprescia, Stelio Z.: Congenital Tuberculosis, N. Y. State J. Med. **42**: 1955, 1942.

The authors present a case of a primiparous, tuberculous woman who was delivered of a premature infant at the seventh month which died twenty-five hours after birth. Autopsy revealed extensive tuberculous lesions in the lungs and also involvement of the spleen, liver, pancreas, adrenals, kidneys and portal and mesenteric lymph nodes. Tubercle bacilli were found in large numbers in the lesions. The placenta was grossly normal, but sections were not studied. This appears to be a true example of congenital tuberculosis. A discussion of the possible tracts by which the infection could gain access to the portal circulation is presented.

KARL M. WILSON.

Young, James: The Eclamptic Phenomenon and Placental Ischaemia, J. Obst. & Gynaec. **49**: 221, 1942.

The author presents his own observations on placental blood changes, infarction, etc., in relationship to toxemias of pregnancy. In the toxemias associated with accidental hemorrhage both the free and the concealed type, Young feels that the bleeding antedates the toxemia. These individuals have usually some bleeding in the early months of pregnancy and are known to have an "abortion taint." This abortion taint when intrinsic in the constitution of toxemic women is antecedent to the toxemia. The fetus is not essential since the same process can occur in hydatid mole. The toxemia develops subsequent to the placental degeneration. It is related to the early stages of the process, and its severity is determined both by the extent of the placental involvement and by the interval during which the fetus survives in utero. Half of the placenta may be compromised before fetal death occurs. In some cases of concealed hemorrhage the toxemia may be grave.

The similarity of the renal lesion, and its clinical manifestations to the "crush syndrome" are also discussed.

WILLIAM BERMAN.

Young, James: Renal Failure After Utero-Placental Damage, Brit. M. J. **4276**: 715, 1942.

Two obstetric conditions showing massive damage of placenta and uterine muscle are followed by renal insufficiency and azotemia. They are accidental hemorrhage and the trauma of labor.

The sequence of events is: (1) Tissue damage. (2) Shock in severe cases, sometimes fatal. (3) Anuria or oliguria, and rising blood urea with diuresis and recovery, or suppression and death. Five fatal cases are reported. They were subjected to clinical and pathologic study. The author has written the following summary: "The foregoing clinico-pathological study of the syndrome in concealed accidental haemorrhage suggests the following proximate causes: (1) The syndrome is determined by a massive utero-placental lesion of ischaemic origin. (2) The renal failure characterized by tubular degeneration and azotaemia is determined by a toxic derived from tissue autolysis. (3) The shock element and the haemolysis which are frequently present may have a similar origin."

FRED L. ADAIR.

Rabin, S., and Dulk, H.: Chorea Gravidarum. A Case Cured by Vitamin B_6, Ann. brasil. de ginec. **14:** 12, 1942.

The authors report a case of a 19-year-old girl in the second month of pregnancy who complained of vomiting. Fifteen days after her first visit, she complained of numbness, weakness and incessant movements of the left arm. Large doses of vitamin B_6 were given and the patient was relieved. Among the thirty-one members of the Brazil Society of Gynecology before whom this case was reported, eight mentioned that they had had sixteen cases of chorea gravidarum. This incidence of chorea may be due to the high frequency of avitaminosis in Brazil.

J. P. GREENHILL.

Corcoran, A. C.: Renal Aspects of the Late Toxemias of Pregnancy, West. J. Surg. **50:** 622, 1942.

Hypertension in pregnancy represents a phase, latent or apparent, in the development of essential hypertension. Experimental renal hypertension with a rigid metal clamp (Goldblatt) parallels the pathologic and clinical findings observed in the human. The maintenance of cardiac output and peripheral blood flow as well as the arteriolar pathology are the same. Induced hypertension in dogs has been shown to be the result of the secretion of renin from the kidney with inadequate blood supply. The reaction of renin with a renin activator in the blood plasma produces an active pressor substance called angiotonin. The injection of angiotonin into dogs or the human will cause arteriolar constriction, increased cardiac effort and elevated blood pressure while peripheral blood flow to the limbs and skin is normal. The action of angiotonin mimics essential hypertension as seen in the human.

A study of changes in the blood flow through the kidneys can be rather accurately determined by diodrast clearance test. The rate of glomerular filtration can be determined by inulin excretion. Using these tests, it has been shown that most hypertensives show some reduction of renal blood flow associated with high filtration fraction. This proves that there is increased intraglomerular pressure which is the result of efferent arteriole constriction. The same phenomena can be reproduced by injection of angiotonin. It has been shown that there is an angiotonin inhibitor substance liberated from the kidneys. Extracts were, therefore, made of kidneys and injected into hypertensive animals and humans with significant but not consistent drops in blood pressure.

Eclamptogenic toxemia is a disease peculiar to pregnancy in the human. It is characterized by decreased rather than increased extraction of water from blood in the glomerulus. Renal blood flow remains normal and since arteriole pressure is increased, one must assume that renal resistance, probably in the arterioles, has been greatly increased. This change is brought about by a swelling of the glomerular basement membranes. This disappears promptly after delivery. The pressor state in eclampsia is apparently of renal origin initiated by some dysfunction of the uterine contents. In contrast to the human, pregnancy in hypertensive dogs has a tendency to lower blood pressure to normal levels with recurrence of the hypertension promptly after delivery.

WILLIAM BICKERS.

Taylor, Howard C., Jr.: Relationship of the Hormones to the Toxemia of Pregnancy, J. A. M. A. **120:** 595, 1942.

The concensus of findings among workers indicate that chorionic gonadotropic substances are elevated in the urine and serum of toxemic patients. The excretion of estrogens has been reported as being low in cases of severe toxemia.

Pregnandiol is low in the urine of toxemia patients according to some reports. As a result of these findings, patients have been treated with hormones both estrogenic and luteal. The findings indicate that neither estrogen or progesterone in any dose yet employed, has shown itself as a specific in the alleviation of the toxic signs of pre-eclampsia. These hormones may, however, exert some influence on a pre-existing toxemia of pregnancy. On the basis of studies made by the author, it appears that sodium and water retention of normal pregnancy is due largely to the steroid hormones manufactured by the placenta. It is doubtful whether the increased sodium retention of toxemia is simply an increase in this effect. The clinical signs of proteinuria, hypertension, and edema appearing in toxemia of pregnancy disappear rapidly during the first days or weeks of the puerperium which may again be conceivably due to the disappearance of the hormones of pregnancy. Other studies involving the anterior pituitary gland, the adrenals, and the thyroid need further study and elucidation.

WILLIAM BERMAN.

Winn, W. C., and Ware, H. Hudnall, Jr.: Hydatidiform Mole: A Report of Six Cases, Virginia M. Monthly **69**: 678, 1942.

Hydatidiform mole occurs once in every 2,000 cases of pregnancy. Color, race and parity are of no importance. The six cases reported are from the obstetric service of the Medical College of Virginia Hospital, one of which was particularly interesting because it was the rare benign, penetrating type, which resulted in spontaneous rupture of the uterus. A review of these six cases leads the author to believe that the uterus is not necessarily enlarged out of proportion to the period of amenorrhea in cases of hydatidiform mole. Toxemia and the beriberi type of heart are frequently associated. The spinal fluid Aschheim-Zondek test is not always positive. Following the removal or expulsion of the mole, the patient should be followed with periodic Friedman tests to rule out the possibility of chorio-epithelioma.

WILLIAM BICKERS.

Tillman, A. J. B.: Classification and Medical Relationship of Hypertensive Albuminuric Pregnancy, J. A. M. A. **120**: 587, 1942.

The author feels that an attempt at an ideal classification of hypertensive albuminuric pregnancy seems at present impossible. It is frequently difficult to establish the origin of the complication. This is especially true when patients present themselves during the last trimester of pregnancy with the findings of hypertension, albuminuria, and edema. Some of these patients had kidney disease before they became pregnant, but it is difficult to establish this fact late in pregnancy. Between the diseases acquired prior to pregnancy, and the convulsive states of pregnancy, there are many phases of hypertension-albuminuria and edema arising in pregnancy which demand clarification. The greatest number of cases consist of pure hypertension. This may arise at any time during pregnancy. One severe type is the sudden, acute severe hypertension which persists in the absence of albumin and edema. Some of these return to normal after delivery, but many of them continue to have hypertensive vascular disease throughout life. Many conditions of hypertensive albuminuric pregnancy cannot be clarified until after delivery. One must conclude that two or more syndromes may arise as a result of pregnancy and terminate in a convulsive state, or that the many syndromes which arise as a result of pregnancy are identical fundamentally.

WILLIAM BERMAN.

Dieckmann, William J., and Kramer, Sylvia: Proteinuria in Toxemia of Pregnancy, J. A. M. A. **120:** 590, 1942.

Normally during pregnancy the same amount of protein appears in the urine as in a normal nonpregnant individual. The incidence of proteinuria in the authors' ante-partum clinic was 20 per cent. Proteinuria usually occurs during labor, especially if the latter is long, the contractions are of long duration and frequent. The cause is the muscular exercise. Infection in the urinary tract may also cause albuminuria. A daily excretion of more than 5 Gm. of protein in the urine for 10 days, or more, should suggest nephritis or nephrosis, as such a large excretion of protein, rarely, if ever, occurs in pre-eclampsia.

Patients with eclampsia excrete a large amount of globulin, and the ratio is 2 or 3 to 1. The protein is excreted through the glomerulus, and as the number of functioning glomeruli grow less, there is less protein excreted. The authors feel that true pre-eclampsia, or eclampsia, do not cause a permanent vascular or renal disorder.

The incidence of abruptio placenta was highest in the hypertensive and the nephritic group. The author treats his patients with high carbohydrate diets of approximately 2,000 calories. The maximum weight gain is adjusted to 7 to 8 kg. for the entire pregnancy. The protein intake should be 80 Gm. or more. Vitamin E has been helpful in preventing fetal death from placental infarction or abruptio placentae. One to three grains of thyroid are given to these patients daily. Salt intake is reduced to a minimum. Water balance is watched. Ammonium chloride in 1 Gm. gelatin capsules is given eight times daily for five days, and repeated after a five-day interval. Oliguria or anuria is treated by hypertonic glucose (20 and 30%) intravenously. The loss of protein should be balanced by diet, but cannot be prevented by increasing the protein intake.

Treatment of these patients depends upon the duration of the pregnancy, the severity of the symptoms and signs of the condition of the cervix. The patient who does not respond to treatment or has been neglected is treated by rupture of the membranes and/or the insertion of a bag if the cervical canal is less than 2 cm. long, or if there is no effacement by cesarean section under local anesthesia.

WILLIAM BERMAN.

Reekie, R. D.: Necrosis of the Anterior Pituitary Associated With Pregnancy and the Puerperium, West. J. Surg. **50:** 293, 1942.

The syndrome of emaciation and death following necrosis of the anterior pituitary is reviewed by the author. It is stated that there was a total of 27 early post-partum necroses, and 21 with healed lesions who died of other causes reported up until 1938. Post-partum necroses occur most commonly after shock secondary to post-partum hemorrhage. Necrosis apparently does not occur following extensive hemorrhage in nonpregnant patients. Pregnancy so alters the blood supply to the anterior pituitary that thrombosis leading to ischemic necrosis may follow severe blood loss at delivery. A case is reported in which a primigravida, who had developed a moderate pre-eclampsia was seized by sudden, severe pain in the dorsolumbar area eight days before term. This was followed by vomiting, headache and convulsions. She was treated conservatively for eclampsia, and on the second day, developed hemorrhagic tendencies at the point of hypodermic needle punctures. Spontaneous labor ensued, and a macerated fetus was delivered approximately 24 hours after the onset of illness. She became anuric, and died in 68 hours after the onset. Autopsy revealed a large retroperitoneal hemorrhage extending from the pelvis up to the right kidney. There were numerous hemorrhagic areas in the skin and extensive necrosis of the anterior lobe of the hypophysis. There were very few histologic changes in the

liver and kidneys. The question is raised as to the cause of death. Is the anterior pituitary necrosis the result of the hemorrhagic diathesis, or may it be considered the etiologic factor in the production of this toxemic syndrome? The relationship of the anterior pituitary to liver function and water balance may be such that a disturbance of pituitary physiology results in widespread disturbances producing the syndrome described here.

WILLIAM BICKERS.

Eastman, N. J., and Whitridge, John: The Prevention of Toxemia of Pregnancy, J. A. M. A. **120** 729, 1942.

The authors mention the declining incidence of maternal mortality due to eclampsia in the United States. These figures are good where good ante-partum care is available. Regular prenatal visits are of prime importance. The changes in blood pressure, weight and albuminuria are again stressed. The authors attach great importance to the education of mothers, in the form of printed matter, concerning the signs of pre-eclampsia and impending eclampsia. The usual dietary and sedative regime is again reviewed. The treatment of these cases depends entirely upon the parity and the duration of pregnancy. The more conservative the method, the better the end results. In eclampsia, the figures leave no doubt that radical treatment is deadly. Great stress is laid on the chronic hypertensive type of toxemia which according to the authors, is about 10 times more frequent now, than 5 years previously. These patients usually have hypertension to some degree before they become pregnant, and their pregnancy aggravates the condition. In this respect, they differ from the eclampsias. The treatment depends upon the severity of the process. The authors warn that in this group of patients, cesarean section should be reserved for severe cases in which conditions are such as to make rupture of the membranes unwise, usually the presence of a firm, long, closed cervix. It should be reserved for cases where difficulty with pelvic delivery is to be anticipated. The repeat toxemia patients, if allowed to go through successive pregnancies, eventually develop chronic vascular damage.

WILLIAM BERMAN.

Urbanski, Adrian X., and Hutner, Cyril I.: Thrombopenic Purpura Complicating Pregnancy, J. A. M. A. **20**: 754, 1942.

The authors report a case of thrombopenic purpura which was followed for 11 years before operation, and 7 years after splenectomy. Before operation, she had many admissions for hemorrhages of one sort or another, and was delivered of a stillborn full-term fetus which manifested general petechial hemorrhages and localized hemorrhages in the skin and in the visceral cavities. Following splenectomy which showed the microscopic picture of thrombopenic purpura, she had three children in a period of six years with no unusual complications of hemorrhage. The first child had a few purpuric spots which disappeared in a few days, but the other two children were entirely normal.

WILLIAM BERMAN.

Vilar, Rafael A.: Malaria in Pregnancy, Bol. Asoc. méd. de Puerto Rico 34: 222, 1942.

Rafael A. Vilar states that many authors think that high fever and toxemia are the principal causes of fetal death in pregnant women who have malarial attacks. But Graham has found the intervillous spaces of the placenta filled with reticulo-endothelial cells instead of blood, and it is therefore possible that many abortions are the result of fetal death due to mechanical obstruction of the ma-

ternal blood in the placenta. The transmission of malaria to the fetus is still uncertain. In any case, malaria is decidedly dangerous for the fetus, and the pregnant woman who has acute or chronic malaria must be treated for her own sake, and for that of the fetus. According to the authorities on the subject, the ideal drug, especially in pregnant women, is quinine. The public and even some physicians are under the impression that quinine is dangerous in pregnancy and may cause abortion. However, most authors agree that in therapeutic doses, the drug does not produce contractions of the uterus and cannot induce premature labor; but if there are already slight uterine contractions, they may be increased by the use of quinine. Plasmochin and atabrin may be prescribed when quinine is contraindicated, but plasmochin is quite toxic and may cause the formation of methemoglobin; it should be given only under strict medical supervision and never alone. Atabrin is less toxic, but large doses may produce lesions of the liver and kidneys which are already under physiologic strain during pregnancy. Consequently, quinine is the drug of choice, and its only contraindication would be an idiosyncrasy of the patient.

J. P. GREENHILL.

Beruti, Joshue A., Diradourian, Jorge and Ahumada, Jorge Luis: Results in the Treatment of Eclampsia, Arch. Clin. obst. y ginec. "Eliseo Cantón" **1**: 69, 1942.

Josue A. Beruti, Jorge Diradourian and Jorge Luis Ahumada have made a statistical study of the cases of eclampsia which were observed in the clinic from 1911 to 1937 inclusive. Among 49,904 pregnancies, there were 339 eclampsia, or 0.67 per cent: 46, or 13.5 per cent, occurred during pregnancy; 220, or 64.8 per cent, during labor, and 73, or 21.5 per cent, during the puerperium. The number of maternal deaths was 64, or 18.8 per cent. Comparison of the treatment used in each of the three stages shows that Stroganoff's method offers the greatest chance of survival for mother and child under all circumstances.

J. P. GREENHILL.

Rose, D. K.: Treatment of Pyelonephritis of Pregnancy, West. J. Surg. **50**: 518, 1942.

Pyelonephritis of pregnancy may be either primary or a recurrence of an old infection. The exacerbation during pregnancy suggests the possibility of some interference with normal drainage in the urinary tract. In such cases a careful urologic search for ureteral stricture, stone, tumor, ureteral kinks, and displacements of the kidney must be made. Drug therapy is never effective in the presence of defective drainage. Lacerations at the time of delivery may damage the trigonal muscle; this results in postpartum urinary stagnation due to the failure of the internal sphincter to properly relax. Micturition is a voluntary-involuntary reflex. Voluntary contraction of the perineal muscles causes a descent of the trigon, which permits urine to escape into the posterior urethra which sets up a reflex stimulating the bladder to contract. This physiology of micturition demands that all anterior vaginal wall lacerations must be repaired from the urethral meatus back to the trigon. In the treatment of pyelitis with acute onset during pregnancy, the author recommends sulfathiazole and sulfadiazine, occasionally mandelic acid in B. coli infections. Postpartum urinary retention is classified under three types: (a) True postpartum, (b) Postoperative, (c) An association of the two. In the post-partum type the bladder fills with a sense of fullness in the lower abdomen, but no sensation of a desire to void; it is a pres-

sure anesthesia. In the postoperative type, there is pain on lowering the perineum and therefore, the patient refrains from doing so; and the subsequent involuntary bladder contraction is prevented. The author points out that urethral caruncle is an effect and not a cause, being always associated with urethrocele or cystocele. He favors intermittent catheterization of the uninfected post-partum bladder only for very short periods of time. If post-partum retention continues, an indwelling catheter should be left in place for several days. Emphasis is placed upon the treatment of the underlying pathology as well as the bacterial infection.

WILLIAM BICKERS.

Veita, Henry R., Schwab, Robert S., and Brazier, Mary A. B.: The Effect of Pregnancy on the Course of Myasthenia Gravis, J. A. M. A. 119: 236, 1942.

The authors review the subject thoroughly and present eight cases of their own. Patients may have both a relapse and a remission during the same pregnancy, the relapse often coming in the first trimester and the remission following. There is usually a complete remission of symptoms in the last two trimesters of pregnancy. When a remission takes place, all symptoms disappear. In general, the relapses during pregnancy are mild to moderate and usually do not cause undue anxiety when the patient is under complete control with prostigmine.

Before the use of prostigmine, abortion was frequently carried out usually at the end of the first trimester. In view of more recent experience with patients under prostigmine therapy, many, if not all, of these abortions would not now be indicated. Abortion, moreover, may not relieve the patient of her symptoms, or even prevent a fatal termination from the disease. In general, either with or without prostigmine, labor itself is not usually affected by the presence of myasthenia gravis. It is concluded that pregnancy, labor, or nursing does not affect the course of the disease unfavorably under present conditions of treatment.

WILLIAM BERMAN.

Leon, Juan, Ferrari, Roberto A., and Gonzalez, Jose Maria Lascano: Grave Intraperitoneal Post-Partum Hemorrhage. Primary Tubal Pregnancy With Uterine Evolution, Bol. soc. de obst. y ginec. de Buenos Aires 20: 731, 1941.

The authors report the case of a primipara, aged 31, who some time previously had an induced abortion with resulting infection which lasted several weeks. Pregnancy and labor were normal, but expulsion of the placenta was delayed. Signs of intra-abdominal hemorrhage appeared but were ignored; Credé's maneuver was performed without result, and the placenta was extracted manually. Exploration of the uterine cavity then disclosed complete rupture on the right side. Subtotal hysterectomy was performed and the patient recovered.

At first thought, it would seem that the previous abortion was the cause of the accident; if the right horn were perforated during curettage and the patient survived, the uterine wall would be friable at this point. But this could not explain the lesions found in the specimen. It could not be an angular or an originally interstitial pregnancy. In favor of the latter were the dilatation of the interstitial portion of the tube and the presence of a corpus luteum on the involved side, but interstitial pregnancy generally causes rupture of the tube during the first months or, if rupture does not occur, the pregnancy continues to develop in the interstitial portion. There is consequently no other recourse but to take the previous curettage into consideration. Probably, the lesion caused by it had changed the anatomic structure and the resistance of the interstitial por-

tion of the right tube, and an interstitial or isthmo-interstitial nidation had occurred on the inflammatorily altered mucosa of the region. The ovum developed toward the uterine cavity where the pregnancy ended normally. During the initial stages of the evolution of the ovum and owing to its implantation, the tubouterine orifice was dilated and kept open by the development of the placenta. After birth, uterine retraction strangulated the tubal portion of the placenta and caused its retention. The rupture may have started during labor or during the contractions to expulse the placenta, and it may have been aggravated by the Credé maneuver; considering the thinning of the tube by stretching and by the action of the chorionic elements, it is surprising that the accident did not occur sooner. Hysterectomy was justified by the difficulty of repairing the large opening in the uterine angle, and by the fact that cuneiform resection could not guarantee satisfactory end results.

J. P. GREENHILL.

Romney, Harry: Treatment of Fracture of Femoral Neck in Pregnancy, Rev. cubana de obst. y. ginec. **4**: 136, 1942.

A 29-year-old woman, in the eighth month of gestation, fractured the neck of the left femur. The fragments were nailed together. Parturition took place without untoward incident and the bone healed quickly. The author does not think pregnancy a contraindication to this method of treating fractures of the femur.

R. J. WEISSMAN.

Puglielli, Mario: The Serious Syndrome of Pernicious Anemia of Pregnancy, Rassegna d'ostet. e ginec. **49**: 479, 1940.

The author presents a detailed case report of an obstetric case, treated in the eighth month of her pregnancy with four transfusions of whole blood, while suffering from a serious complication diagnosed as pernicious anemia of pregnancy. The author reviews several theories of the pathogenesis regarding this complication of pregnancy.

CLAIR E. FOLSOME.

Puerperium

Collins, Conrad G., Jones, Jack R., and Nelson, Edward W.: Surgical Treatment of Pelvic Thrombophlebitis, New Orleans M. and S. J. **95**: 324, 1943.

The high mortality associated with pelvic thrombophlebitis and the poor results obtained by conservative treatment, prompted the authors to adopt a radical surgical treatment. They have reported three cases treated by ligation of the ovarian veins and the inferior vena cava. In the first case, pelvic thrombophlebitis followed a low forceps delivery, fever and chills beginning on the seventh day. Using spinal anesthesia, the right ovarian vessels were ligated and the inferior vena cava ligated one inch proximal to the junction of the common iliacs. The second case followed a septic abortion. The third case followed a vaginal hysterectomy. In all cases, the temperature came to normal soon after ligation of the inferior vena cava. Although venous pressure in the lower extremities was elevated following operation, no edema developed. Postoperative sympathetic procaine block of the sympathetic chain is recommended to aid in the development of collateral circulation and relieve edema that might be found after operation.

WILLIAM BICKERS.

Ricci, Guido: Parametrium and Pelvic Cellular Tissue. Topographic, Physiopathologic and Symptomatologic Study, Bol. soc. de obst. y. ginec. de Buenos Aires **21:** 402, 1942.

Discussing the physiopathology of the parametrium and the pelvic cellular tissue, Ricci points out the correlation between varicosities of the lower extremities and genitalia and parametrial lesions, the latter probably being the starting point for the former. Attention is called also to the syndrome of "pseudophlebitis" consequent to a parametrial process, which is to be differentiated from phlegmasia alba dolens by the absence of the venous cord and of pain in the femoral region.

In examining the parametrium, the author prefers monomanual to bimanual palpation, claiming that the finger in the vagina is the one which receives the best orientation with the least traumatization. Bimanual palpation should be complementary only, to finally establish the topographic relations of the parametrium with the structures above it. The examination of the anterior parametrium is completed by introducing a rigid metallic sound into the urethra thus facilitating vaginal digital examination. Rectal palpation and a combined rectovaginal examination is recommended for examination of the posterior parametrium. Regarding the examination in acute parametritic processes, Ricci maintains that when examination is done with one finger with utmost care and gentleness, the danger is purely speculative, while the information obtained is of paramount value. Clinical examination of the parametrial tissues should be supplemented by radiography of the colon, hysterography, cystoscopy, rectoscopy and, if necessary, by exploratory puncture.

J. P. GREENHILL.

Leopoldo, Perez Rojas: Prophylaxis and Treatment of Puerperal Infection, Rev. cubana de obst. y ginec. **4:** 199, 1942.

Leopoldo Perez Rojas states that 21,101 patients were delivered at the Municipal Maternity "America Arias" of Havana from 1937 to 1941. There were one hundred cases of puerperal infection, with eight deaths, or 8 per cent of the infected cases and 0.037 per cent of the total number of deliveries. Five of the patients who died were already infected on admission; the other three had had symphysiotomies.

Puerperal infection was greatly decreased under the influence of simple general prophylactic measures. Preventive treatment, without waiting for the appearance of signs of infection in any woman with more or less complicated labor ending with a difficult intervention, will decrease obstetric morbidity; prophylactic chemotherapy is used at the Municipal Maternity. There are no aseptic labors in the bacteriologic sense of the term, because many pregnant women carry in their genital tract organisms living as saprophytes which, during labor and the puerperium, become virulent as the defenses of the body decrease; another cause is genital metastasis from a remote focal infection (tonsillitis, grippe, etc.) or spreading of a neighboring infection by the lymphatic route. Therefore, sulfamide chemotherapy is used to combat the endogenous infections which may arise. In labors over 24 hours' duration, premature rupture of the membranes, vaginal examination, etc., sulfamides are given before delivery in doses of 5 to 6 Gm. a day, to maintain a concentration of 6 to 8 mg. per 100 c.c. in the blood. Oxytocics are also given during the post partum. The small amounts of the drugs eliminated in the milk do not contraindicate nursing.

J. P. GREENHILL.

Correspondence

The Reaction of the Human Uterus to Epinephrine

To the Editor:

I have read with interest the letter of Dr. Rucker in the August, 1943 issue of the *American Journal of Obstetrics and Gynecology* (page 330) regarding our report on the reaction of the human uterus to epinephrine. I particularly appreciate his constructive criticism, for he speaks from the wide experience of 91 cases of contraction rings; my own obstetric experience in the supervision of 7,000 deliveries has afforded me the opportunity to see only one and perhaps one other mild case of contraction ring dystocia. The combined experience of the diplomates of the American Board of Obstetrics and Gynecology on the staff of the University of Nebraska is 8 cases in 27,000 deliveries. Apparently the incidence of this condition varies widely. Either there has been an epidemic of contraction rings in Dr. Rucker's community, or his obstetric experience has included an astronomical number of deliveries.

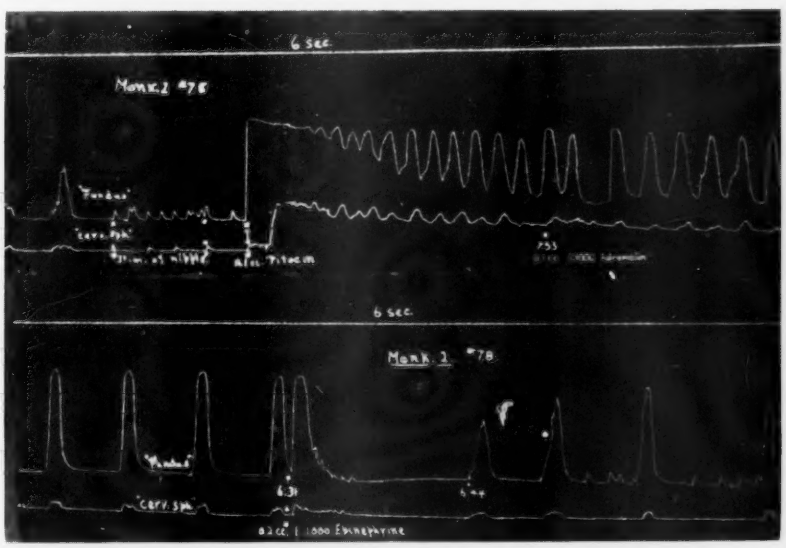

Fig. 1.—Photostatic copy of a chart of monkey uterus published by Ivy, et al.: in Am. J. Obst. & Gynec. 22: 396, 1931.
This chart is an intrauterine tracing of a monkey showing both fundal and cervical contractions.
In both sections of the tracing the uterus reacts by premature contractions, followed by compensatory pause. This pause is approximately equal to the dropped beat. Also note that the cervix follows the fundus.

I am sorry that Dr. Rucker does not approve of India ink tracings for publication; however, if he will refer to his own published "originals" in the *Southern Medical Journal* **18**: 912, 1925, it is noted that they have been reproduced so poorly that no other investigator can study them critically. Also, it will be noted that these patients received a number of drugs (adrenalin, novocain, hyoscine, chloral hydrate, paraldehyde, pituitrin, and quinine) so that it becomes impossible to interpret how much of the observed response was due to the adrenalin *alone*. Our experience in experimental work has convinced us of the impossibility of interpreting observations made during the administration of a multiplicity of drugs.

Apparently from Dr. Rucker's letter he failed to look up published graphs of Ivy, Woodbury, or Bourne. We had requested that these graphs* be republished with our paper for comparison but this seemed undesirable. If these graphs are compared with those of our study, it is seen that they are very similar if not identical. In each case there is an extra contraction of the uterus followed by a pause. We interpret these graphs to indicate that the uterus responds to ad-

Fig. 2.—A composite graph of pressures in which the lower tracing represents the net intrauterine pressures. Photostatic copy taken from work published by WOODBURY, et al.: *Am. J. Physiol.* **121**: 648, 1938.

While this study was done on intact human uteri, it was not designed to demonstrate uterine contractions per se, but rather uterine tone. In the bottom curve of this graph one notes the effect of the injection of adrenalin. There is a rise in uterine tone followed by 2 uterine contractions and the fall in uterine tone. In the text Dr. Woodbury states:

> "The effect of intravenous administration of 0.1 mg. epinephrine hydrochloride (see Fig. 13) is to produce a marked rise in blood pressure and intra-uterine pressure. The uterine contraction is stronger and much more abrupt in onset than the normal contractions. . . . The relaxation is slower is anything than normal and followed by two quickly succeeding smaller contractions. After this response uterine excitability seems somewhat lessened to return soon to normal."

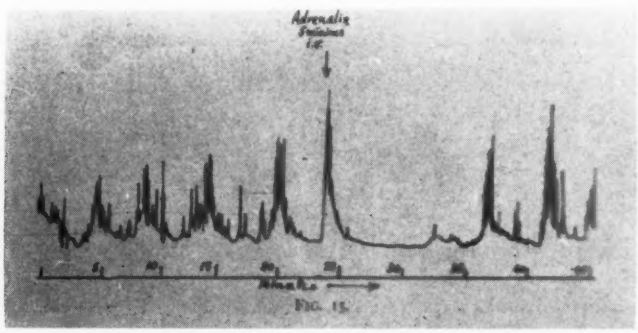

Fig. 3.—Photostatic copy of a graph published by BOURNE, et al., on human uterine strips published in the *J. Obst. and Gynaec. Brit. Emp.* **34**: 272, 1928.

In the text these authors state:

> "Nevertheless, the view that adrenalin exercises an inhibitory effect on the pains of labour, required for its support less equivocal evidence than this, and in another patient, in whom we recorded a rapid succession of six pains during 25 minutes, an injection of five minims of adrenalin was made into the median vein. This injection (see Fig. 15) was followed by a complete cessation of uterus contractions during 12 minutes, after which the pains began again."

I accept the graphs of Dr. Bourne; but I am inclined to differ with him on the interpretation. If you will take a ruler and draw the peak lines of uterine contraction you see at once that the contraction stimulated by adrenalin is displaced in rhythm and augmented in intensity. The so-called 12-minute refractory period represents approximately 2 uterine contractions, so that we have in effect only one dropped beat.

It is my impression that this inhibition is a refractory state in the muscle due to muscular activity rather than to the adrenalin itself, for in each circumstance this period of inhibition is approximately the same length (2 uterine contractions). This inhibitory state is always preceded by an extra contraction.

*These graphs are reproduced here for comparison.

renalin by contractions, and that the apparent inhibition is a compensatory pause resulting from muscular activity.

After these graphs have been studied by Dr. Rucker we would appreciate having his interpretation of the curves.

As I read the letter it appears that our differences of opinion are primarily a question of clinical interpretation. To this we are entitled. I would be very much interested in Dr. Rucker's experience with adrenalin *alone without any other form of treatment or interference* (anesthesia, sedation, parenteral fluids, forceps, version and extraction, bag). His wide experience of 91 cases of contraction ring dystocia has afforded him a privilege which few others have had to study the action of adrenalin alone. May I inquire how often he has used adrenalin *alone* and with what results?

WILLIS E. BROWN, M.D.

OMAHA, NEB.
SEPTEMBER 16, 1943.

Reply From Dr. Rucker

To the Editor:

Your favor of September 27, requesting a reply to Dr. Brown's letter came in due time. I am sorry that I have taken so long to answer it.

In regard to the first of the two questions, interpreting Dr. Brown's graphs and those of Ivy, Bourne, and Woodbury, I would say that without seeing the patient at the time the graphs were made, their interpretation would be as difficult as giving an opinion on a microscopical section of tissue without knowing something of the history of the patient. In the *Journal of Laboratory and Clinical Medicine* (**10**: 390, 1925), I discussed some of the difficulties of interpreting hysterograms and showed that extraneous and extrauterine phenomena cause tremendous differences in uterine pressure, as shown on the hysterogram: I also showed that a psychic influence frequently had marked effect. Fig. 13 of the article shows a hysterogram in which there is a cessation of uterine contractions following an attempt at giving caudal anesthesia. I was unable to locate the sacral hiatus and gave the patient no drug whatever, nevertheless, the contractions ceased for 28 minutes. Furthermore, this article inadvertently shows another complication that might occur as there is a mixup of the figures and legends. The printer changed them about so that Fig. 11 which reads "Internal hysterogram showing cessation of uterine contraction for an hour and 15 minutes after sacral anesthesia with novocain and adrenalin," with no cessation. Fig. 12 shows the cessation of contractions for one hour and 15 minutes. Because of these difficulties, I would hesitate to offer an interpretation of graphs by such authorities. However, I do feel that one-half minim of adrenalin is an inadequate dose upon which to base an opinion that adrenalin does not cause a pregnant uterus to relax.

As to the second question, i.e., the number of times I have used adrenalin alone and the response of the uterus to adrenalin, it would be quite difficult to answer this question categorically as this work was done nearly twenty years ago, and no cross-reference was kept of the records so that it would be practically impossible to get out all the cases that were studied. In my article in the *Southern Medical Journal* (**17**: 412, 1925), I reported the first cases that I studied in reference to the effect of adrenalin. Case 3 had no previous medication. Case 5 had only a proctoclysis of 5 per cent glucose solution previous to the administration of adrenalin which was followed by cessation of contractions for 30 minutes. Case 7 had no previous medication and had no effect from adrenalin. Case 8 had no previous medication and had a definite diminution of contractions after 2 minims of adrenalin, hypodermically. Case 9 had no previous medication and had a definite diminution of the strength of contractions after adrenalin. Case 10,

that of an abortion on account of pyelitis, had no previous medication and no appreciable effect from adrenalin. Case 11 had glucose per rectum previously, and after adrenalin the contractions ceased for 26 minutes. Case 12 had no previous medication and after adrenalin there was a diminution in the strength of contractions. Case 16 had no previous medication. After adrenalin the contractions were of less force for ten minutes.

I think this also covers the supplementary question as to the length of time that the uterus remains quiescent after administration of adrenalin.

M. P. RUCKER, M.D.

RICHMOND, VA.
OCTOBER 22, 1943.

Final Note From Dr. Brown

To the Editor:

There are two points of interest in Dr. Rucker's letter of October 22, 1943.

The first relates to the psychic and other factors which he suggests influence uterine contractions. It would be a most unusual coincidence if the same set of extraneous circumstances prevailed in Mr. Bourne's labor room in England in 1927, in an anesthetized monkey in Dr. Ivy's laboratory in Chicago in 1931, in Dr. Woodbury's studies of laboring patients in Atlanta, Georgia, in 1937, and in post-partum patients in Omaha in 1941. The dosage of epinephrine has varied widely with each of these investigations (from ½ to 6 minims).

Nevertheless, the curves of each of the four investigators are the same.

The second point is covered in Dr. Rucker's last paragraph and becomes self-explanatory when reduced to chart form.

EFFECT OF ADRENALIN ON UTERINE CONTRACTIONS
(WITHOUT OTHER MEDICATION)

	INHIBITION	DOUBTFUL	NO EFFECT
CASE NO.	3-5-11	8-9-16	7-10
%	36%	36%	28%

Thus when epinephrine is used alone it exhibits very doubtful inhibitory effect.

WILLIS E. BROWN, M.D.

OMAHA, NEB.
NOVEMBER 3, 1943.

Society Transactions

THE NEW YORK OBSTETRICAL SOCIETY

MEETING OF OCT. 12, 1943

The following papers were presented:

An Unusual Intra-abdominal Surgical Complication in the Puerperium. Edwin G. Langrock, M.D.

Surgical Complications During Pregnancy. Charles G. Child, III, M.D. (by invitation) and R. Gordon Douglas, M.D. (For original article, see page 213.)

THE OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF JUNE 5, 1943

A special meeting to commemorate the Seventy-Fifth Anniversary of the Founding of the Society.

The Program consisted of the following papers:

The History of the Society. Lewis C. Scheffey, M.D.

Personal Reminiscences. Daniel Longaker, M.D.

The Present Status of the Society. John C. Hirst, M.D.

The Future of the Society. Edward A. Schumann, M.D.

Necrology

SAMUEL HERBERT GEIST, A.B., M.D., gynecologist, died in New York City, December 14, 1943, at the age of 58. He was a graduate of the College of Physicians and Surgeons, Class of 1908, interned at Mt. Sinai Hospital in New York, with which he was continuously associated, until the time of his death, since 1937 as Attending Gynecologist. He served as Captain in the Army Medical Corps with the American Expeditionary Forces in France, 1917-1918. Well known for his research work in the field of hormones and ovarian tumors, he was the author of an extended textbook on the latter which was published recently.

Item

American Board of Obstetrics and Gynecology, Inc.

Examinations

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 12, 1944, at 2:00 P.M.

Arrangements will be made so far as is possible for candidates in military service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or some responsible person designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates for the February 12, 1944, Part I examination, who are entering Military Service, or who are now in Service and may be assigned to foreign duty, may submit their case records in advance of the above date, by forwarding them to the office of the Board Secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

All candidates will be required to take both the Part I examination, and the Part II examination (oral-clinical and pathology examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year.

Headquarters for the Part II examination will be the Hotel William Penn, Pittsburgh, Pennsylvania, from June 7 to 13, 1944. Notice of the exact time of the examinations will be sent all candidates well in advance of the examination date. Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of our published regulations as they apply to civilian candidates.

Applications for the 1944 examinations are now closed.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

DECEMBER 18, 1943. PAUL TITUS, M.D.